ISSN 2782-9510

PEDIATRIC INFECTIOUS DISEASE SOCIETY OF THE PHILIPPINES

# PIDSP JOURNAL

**Vol. 23 No. 2**
**July - December 2022**

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 2-4 July-December 2022
Dy-Co AS. Baby Steps, Giant Strides
https://doi.org/10.56964/pidspj20222302002

EDITORIAL

# BABY STEPS, GIANT STRIDES

*Arlene S. Dy-Co, MD*
*Editor-in-Chief, PIDSP Journal*

This is the second time we are releasing a joint editorial from journals all over the world in the call for action to address climate change. The COVID-19 pandemic has caught the world unaware despite the progress in science; majority did not take the warnings of a looming pandemic. With climate change, its impact on infectious diseases will not be any gentler as the hazards are too numerous. From increased transmission of infections, expansion of infections to other geographic areas and emergence of new infectious diseases. This would be gargantuan compared to a pandemic as this would not only involve one infectious disease but numerous and would impact every aspect of the world we know. Joining this call for action is a baby step, but no action is too small in whatever way we can to help ensure a better Earth for our younger generation.

Our giant stride for this issue comes with the news that our published articles will now have digital object identifier (DOI). The Pediatric Infectious Disease Society of the Philippines Journal is proud to announce as we join the more than 10,000 organizations that assigns DOI names. The DOI is a unique alphanumeric string assigned by an international registration agency and will provide persistent identification of our articles. This will make our published articles easy to find, cite, link, assess and reuse, thus making scholarly communications more effective. Likewise, this increases opportunities for transparency in scholarly works. Technology has changed publishing dramatically and keeping up with this from the local forefront is not easy. We believe that we will be closer to the realization of making our local publications more visible and discoverable by a wider audience with this giant stride.

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Vol 23 No 2, pp. 5-8 July-December 2022
Atwoli L, Erhabor GE, Gbakima AA, Haileamlak A, Ntumba JMK, Kigera J, *et al*. COP27 Climate Change Conference: Urgent Action Needed for Africa and the World

**JOINT EDITORIAL**

# COP27 CLIMATE CHANGE CONFERENCE: URGENT ACTION NEEDED FOR AFRICA AND THE WORLD

*Wealthy nations must step up support for Africa and vulnerable countries in addressing past, present and future impacts of climate change*

Lukoye Atwoli, Editor-in-Chief, *East African Medical Journal*; Gregory E. Erhabor, Editor-in-Chief, *West African Journal of Medicine*; Aiah A. Gbakima, Editor-in-Chief, *Sierra Leone Journal of Biomedical Research*; Abraham Haileamlak, Editor-in-Chief, *Ethiopian Journal of Health Sciences*; Jean-Marie Kayembe Ntumba, Chief Editor, *Annales Africaines de Medecine;* James Kigera, Editor-in-Chief, *Annals of African Surgery*; Laurie Laybourn-Langton, University of Exeter; Bob Mash, Editor-in-Chief, *African Journal of Primary Health Care & Family Medicine*; Joy Muhia, London School of Medicine and Tropical Hygiene; Fhumulani Mavis Mulaudzi, Editor-in-Chief, *Curationis*; David Ofori-Adjei, Editor-in-Chief, *Ghana Medical Journal*; Friday Okonofua, Editor-in-Chief, *African Journal of Reproductive Health*; Arash Rashidian, Executive Editor, and Maha El-Adawy, Director of Health Promotion, *Eastern Mediterranean Health Journal*; Siaka Sidibé, Director of Publication, *Mali Médical*; Abdelmadjid Snouber, Managing Editor, *Journal de la Faculté de Médecined'Oran*; James Tumwine, Editor-in-Chief, *African Health Sciences*; Mohammad Sahar Yassien, Editor-in-Chief, *Evidence-Based Nursing Research*; Paul Yonga, Editor-in-Chief, *East African Medical Journal*; Lilia Zakhama, Editor-in-Chief, *La Tunisie Médicale*; and Chris Zielinski, University of Winchester

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The 2022 report of the Intergovernmental Panel on Climate Change (IPCC) paints a dark picture of the future of life on earth, characterised by ecosystem collapse, species extinction, and climate hazards such as heatwaves and floods.[1] These are all linked to physical and mental health problems, with direct and indirect consequences of increased morbidity and mortality. To avoid these catastrophic health effects across all regions of the globe, there is broad agreement—as 231 health journals argued together in 2021—that the rise in global temperature must be limited to less than 1.5°C compared with pre-industrial levels.

While the Paris Agreement of 2015 outlines a global action framework that incorporates providing climate finance to developing countries, this support has yet to materialise.[2] COP27 is the fifth Conference of the Parties (COP) to be organised in Africa since its inception in 1995.

Ahead of this meeting, we—as health journal editors from across the continent—call for urgent action to ensure it is the COP that finally delivers climate justice for Africa and vulnerable countries. This is essential not just for the health of those countries, but for the health of the whole world.

## Africa has suffered disproportionately although it has done little to cause the crisis

The climate crisis has had an impact on the environmental and social determinants of health across Africa, leading to devastating health effects.[3] Impacts on health can result directly from environmental shocks and indirectly through socially mediated effects.[4] Climate change-related risks in Africa include flooding, drought, heatwaves, reduced food production, and reduced labour productivity.[5]

Droughts in sub-Saharan Africa have tripled between 1970-79 and 2010-2019. In 2018, devastating cyclones impacted three million people in Malawi, Mozambique and Zimbabwe.[6] In West and Central Africa, severe flooding resulted in mortality and forced migration from loss of shelter, cultivated land, and livestock.[7] Changes in vector ecology brought about by floods and damage to environmental hygiene has led to increases in diseases across sub-Saharan Africa, with rises in malaria, dengue fever, Lassa fever, Rift Valley fever, Lyme disease, Ebola virus, West Nile virus and other infections.[8,9] Rising sea levels reduce water quality, leading to water-borne diseases, including diarrhoeal diseases, a leading cause of mortality in Africa.[8] Extreme weather damages water and food supply, increasing food insecurity and malnutrition, which causes 1.7 million deaths annually in Africa.[10] According to the Food and Agriculture Organization of the United Nations, malnutrition has increased by almost 50% since 2012, owing to the central role agriculture plays in African economies.[11] Environmental shocks and their knock-on effects also cause severe harm to mental health.[12] In all, it is estimated that the climate crisis has destroyed a fifth of the gross domestic product (GDP) of the countries most vulnerable to climate shocks.[13]

The damage to Africa should be of supreme concern to all nations. This is partly for moral reasons. It is highly unjust that the most impacted nations have contributed the least to global cumulative emissions, which are driving the climate crisis and its increasingly severe effects. North America and Europe have contributed 62% of carbon dioxide emissions since the Industrial Revolution, whereas Africa has contributed only 3%.[14]

**The fight against the climate crisis needs all hands on deck**

Yet it is not just for moral reasons that all nations should be concerned for Africa. The acute and chronic impacts of the climate crisis create problems like poverty, infectious disease, forced migration, and conflict that spread through globalised systems.[6,15] These knock-on impacts affect all nations. COVID-19 served as a wake-up call to these global dynamics and it is no coincidence that health professionals have been active in identifying and responding to the consequences of growing systemic risks to health. But the lessons of the COVID-19 pandemic should not be limited to pandemic risk.[16,17] Instead, it is imperative that the suffering of frontline nations, including those in Africa, be the core consideration at COP27: in an interconnected world, leaving countries to the mercy of environmental shocks creates instability that has severe consequences for all nations.

The primary focus of climate summits remains to rapidly reduce emissions so that global temperature rises are kept to below 1.5°C. This will limit the harm. But, for Africa and other vulnerable regions, this harm is already severe. Achieving the promised target of providing $100bn of climate finance a year is now globally critical if we are to forestall the systemic risks of leaving societies in crisis. This can be done by ensuring these resources focus on increasing resilience to the existing and inevitable future impacts of the climate crisis, as well as on supporting vulnerable nations to reduce their greenhouse gas emissions: a parity of esteem between adaptation and mitigation. These resources should come through grants not loans, and be urgently scaled up before the current review period of 2025.

They must put health system resilience at the forefront, as the compounding crises caused by the climate crisis often manifest in acute health problems. Financing adaptation will be more cost-effective than relying on disaster relief.

Some progress has been made on adaptation in Africa and around the world, including early warning systems and infrastructure to defend against extremes. But frontline nations are not compensated for impacts from a crisis they did not cause. This is not only unfair, but also drives the spiral of global destabilisation, as nations pour money into responding to disasters, but can no longer afford to pay for greater resilience or to reduce the root problem through emissions reductions. A financing facility for loss and damage must now be introduced, providing additional resources beyond those given for mitigation and adaptation. This must go beyond the failures of COP26 where the suggestion of such a facility was downgraded to "a dialogue."[18]

The climate crisis is a product of global inaction, and comes at great cost not only to disproportionately impacted African countries, but to the whole world. Africa is united with other frontline regions in urging wealthy nations to finally step up, if for no other reason than that the crises in Africa will sooner rather than later spread and engulf all corners of the globe, by which time it may be too late to effectively respond. If so far they have failed to be persuaded by moral arguments, then hopefully their self-interest will now prevail.

This Comment is being published simultaneously in multiple journals. For the full list of journals see: https://www.bmj.com/content/full-list-authors-and-signatories-climate-emergency-editorial-october-2022

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Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 9-18 July-December 2022
Cano CU, Ignacio LADD, Rodriguez EV, Vinuya FVG, Garcia RDJ and Regalado JA. Multi-System Inflammatory Syndrome in Neonate (MIS-N) Presenting as Bowel Obstruction: A Case Report
https://doi.org/10.56964/pidspj20222302004

CASE REPORT

# MULTI-SYSTEM INFLAMMATORY SYNDROME IN NEONATE (MIS-N) PRESENTING AS BOWEL OBSTRUCTION: A CASE REPORT

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## ABSTRACT

**Background:** Since the start of SARS-CoV-2 pandemic, a post-infection hyperinflammatory process in children with features similar to Kawasaki disease, termed multisystem inflammatory syndrome in children (MIS-C),[1] was identified. Thousands of MIS-C cases have already been reported worldwide.[2] As possible cases of MIS-C in neonates were increasingly identified, multisystem inflammatory syndrome in neonates (MIS-N) as a distinct entity was proposed as neonates may not manifest all the typical features described in older children.

**Case Presentation:** We describe the case of a previously well term neonate with sudden signs of bowel obstruction who later had multisystem involvement (cardiac, gastrointestinal, and hematologic). The baby was born to a 23-year-old multigravida with an unremarkable prenatal history except for COVID-19 infection during her 34$^{th}$ week age of gestation. The mother presented with mild respiratory symptoms and resolved with supportive management. Our patient was born stable, then had sudden manifestations of feeding intolerance on the 16$^{th}$ day of life and upon work-up had moderate anemia, elevated inflammatory and cardiac markers, ileus, and dilatation of proximal left coronary artery. RT-PCR for SARS-CoV2 was negative. The baby was managed with intravenous immunoglobulin (IVIG) and steroids, with rapid clinical and laboratory parameters improvement thereafter.

**Conclusion:** MIS-N is still evolving as a disease entity with no clear, directed guidance yet on diagnosis and management. Management is extrapolated from treatment of MIS-C. Additional case reports and series are warranted to increase awareness and enable better understanding of the disease pathology among clinicians for timely investigation, diagnosis, and management.

**KEYWORDS:** *Neonatal, Multi-System Inflammatory Syndrome (MIS-N), SARS-CoV-2, Case Report*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

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## INTRODUCTION

Since the start of SARS-CoV-2 pandemic, a post-infection hyperinflammatory process in children with features like Kawasaki disease was identified. The disease process is labelled as multisystem inflammatory syndrome in children (MIS-C), defined by the US Centers for Disease Control and Prevention as a disease entity of sufficient severity to warrant hospitalization in individuals < 21 years, characterized by the presence of fever, laboratory evidence of inflammation and multisystem organ dysfunction, with temporal association to recent SARS-CoV-2 infection, and absence of other plausible alternate diagnoses.[1] Thousands of MIS-C cases have already been reported worldwide.[2] As possible cases of MIS-C in neonates were increasingly identified, multisystem inflammatory syndrome in neonates (MIS-N) as a distinct entity was proposed, as neonates may not manifest all the typical features described in older children. To date, there are eight case reports[2-9] and two case series[10-11] on neonatal multisystem inflammatory syndrome published, with various case inclusion criteria adapted from the CDC definition of MIS-C and modified to account for the mode of disease acquisition and physiology (i.e., underdeveloped pyretic response) unique among neonates. Majority of the neonates described were symptomatic within the first week of life and presented predominantly with respiratory or cardiac involvement. In this report, we describe the case of a 16-day old previously well term neonate with sudden signs of possible bowel obstruction, later noted to have multisystem involvement and managed as a case of MIS-N.

## CASE PRESENTATION

A singleton male infant was born to a 23-year-old G2P1 (1001) non-smoker and non-alcoholic beverage drinker on her 39 1/7 weeks AOG via repeat caesarean section.

The mother had COVID-19 infection confirmed via COVID-19 RT-PCR at 34 weeks AOG with mild respiratory symptoms, and was managed with Vitamin C + Zinc for two weeks and home isolation for 10 days. She completed two doses of COVID-19 vaccination prior to her illness. There was no maternal history of hypertension, diabetes mellitus, and bacterial or fungal infection. HBsAg, VDRL, and HIV tests were all non-reactive. The mother had regular intake of vitamins with no exposure to any teratogen or radiation. The baby was born live, term, singleton male, via repeat caesarean section, with APGAR score of 9 and 9, Ballard score of 39 weeks, with birthweight of 3355g (7 lbs 6 oz), birth length of 49.5cm, and was assessed as being appropriate for gestational age. He was discharged stable with the mother on the second hospital day, with good cry and good latch, jaundice up to the chest, and with adequate urine output and bowel movement within the first 24 hours of life. Since the baby was asymptomatic at birth, RT-PCR for SARS-CoV2 was not indicated. The newborn hearing screening and critical congenital heart disease screening results were normal. At home, the baby tolerated direct breastfeeding, but was started on mixed feeding on the 8th day of life due to inadequate maternal breastmilk supply. There was adequate urine output and bowel movements, with no hypothermic or hyperthermic episodes, no rapid progression of jaundice, and no jitters nor cyanosis noted. Newborn screening results later came back normal. Family history revealed hypertension, diabetes mellitus, and colon cancer on the paternal side. Social and environmental histories were non-contributory. He was taken cared for by both parents who were both fully immunized with COVID-19 vaccines and were asymptomatic. There was no travel history for the family since the baby was discharged from the hospital.

On the 16th day of life, the baby was noted to be pale-looking, with no signs of overt bleeding, with one hyperthermic episode (temperature of 38$^{o}$C). The baby also started having postprandial vomiting of initially brownish and, later, bilious in colour.

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https://doi.org/10.56964/pidspj20222302004

Upon arrival at the ER, the baby was awake with fair cry and activity, and with good suck on gloved finger. He was thermoregulated at 36.5°C, HR was at 145 bpm, RR was at 48 cpm, and oxygen saturation at 98% at room air. There was generalized pallor, no rash, and no swelling nor erythema of the palms and soles. The baby had flat fontanelles and no conjunctival injection, lips were slightly pale and dry, buccal mucosa was moist, and there was no strawberry tongue. There were no signs of respiratory distress. Cardiac examination revealed distinct regular heart sounds with no murmur. Abdomen was soft, non-distended, with normal bowel sounds and no palpable mass nor organomegaly. Pulses were full and equal, and there was no peripheral cyanosis. Neurologic examination was essentially unremarkable. The admitting impression was late-onset neonatal sepsis versus Multisystem Inflammatory Syndrome in Neonate (MIS-N), given the history of maternal COVID-19 infection during late pregnancy, to rule out bowel obstruction. On admission, the baby was kept on nothing per orem and intravenous (IV) fluids were started. Orogastric tube (OGT) was inserted and yielded 40ml of bilious fluid. Capillary blood sugar (CBG) was normal. Nasopharyngeal swab for COVID-19 RT-PCR showed negative results. Complete blood count (CBC) showed decreased hemoglobin, normal WBC count, and thrombocytosis (see Table 1). Abdominal radiograph showed an impression of adynamic ileus (see Figure 1A and 1B). Electrolyte levels were normal. Antibiotics (cefotaxime and amikacin) were started. D-dimer, CRP and CPK-MB were more than 3x elevated while Pro-BNP was 15x elevated than normal and Troponin-I showed high risk results (see Table 1). Procalcitonin level was normal. The unexplained anemia with no identified source of bleeding prompted further work-up. Corrected reticulocyte count was normal and peripheral blood smear showed decreased and normocytic and normochromic RBC with some anisopoikilocytosis. There was normal WBC with lymphocytic predominance and increased platelet count.

Packed RBC transfusion (10ml/kg) was ordered to correct the anemia; however, a major incompatibility with the same blood type (blood type A+) was found, despite negative direct and indirect Coomb's test results. Compatible packed RBC of blood type O+ was later transfused with no untoward events. 2-D echocardiogram revealed proximal left coronary artery dilatation with a maximal intra-luminal diameter of 0.20cm, good left ventricular systolic and diastolic functions (ejection fraction of 68%), normal pulmonary arterial pressure and no pericardial effusion (see Figure 2). 15L-ECG revealed normal sinus rhythm with probable right ventricular hypertrophy (see Figure 3). Chest radiograph showed clear lungs with no cardiomegaly. Despite the presence of spontaneous bowel movements and being on NPO, there was persistence of bilious output per OGT. Repeat abdominal radiograph was done the next day showing no significant change in ileus (see Figure 1C and 1D). The diagnosis of MIS-N was made on day 2 of hospitalization, and intravenous immunoglobulin (IVIG) (2gm/kg/dose), IV methylprednisolone (2mg/kg/day, every 12 hours) and IV omeprazole were started. Urinalysis was negative for urinary tract infection, but urine culture grew 10,000 colony-forming units/ml of *Klebsiella pneumoniae* for which antibiotics were continued. OGT yielded minimal clear output on the 3rd to 4th hospital days. With the elevated D-dimer and 2-D echocardiogram findings, low dose acetyl-salicylic acid (ASA) (1.6mg/kg/day) was also commenced on the 4th hospital day as soon as feeding was started.

Post-IVIG and packed RBC transfusion, repeat laboratory tests done on the 5$^{th}$ hospital day showed improved hemoglobin and hematocrit, although still decreased as compared to the normal values for age. Leucocytosis, likely secondary to giving of steroids, along with reactive thrombocytosis were noted. Inflammatory and cardiac markers showed significantly decreased levels from the previous levels (see Table 1). Antibiotics were discontinued after three days as blood culture showed no growth.

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IV methylprednisolone was given for three days and was shifted to oral prednisone (1mg/kg/day), while IV omeprazole was shifted to oral esomeprazole. The baby was discharged stable on the 6th hospital day, tolerating expressed breastmilk, pinkish in color with good cry and activity.

He had adequate urine output and spontaneous bowel movements. Low dose ASA was continued and prednisone was tapered over four weeks. Esomeprazole was continued while he was on ASA and prednisone. The baby was scheduled for repeat 2D echo two months later that revealed normal results.

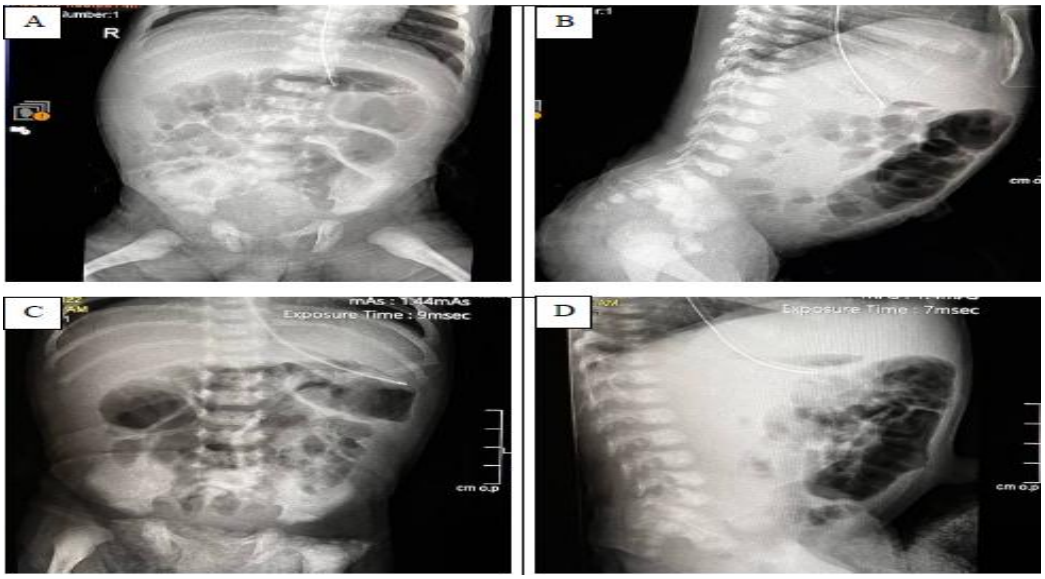


Figure 1. (A) and (B) Abdominal radiographs taken during first hospital day showed presence of gas-dilated loops of bowels, disorganized in pattern with no evidence of pneumoperitoneum. Impression: To consider adynamic ileus. (C) and (D) Abdominal radiographs on the second hospital day showed no significant change in the degree and number of gas filled bowel loops. Neither high-grade obstruction nor evidence of pneumoperitoneum was seen. Impression: No significant change in presumed ileus.

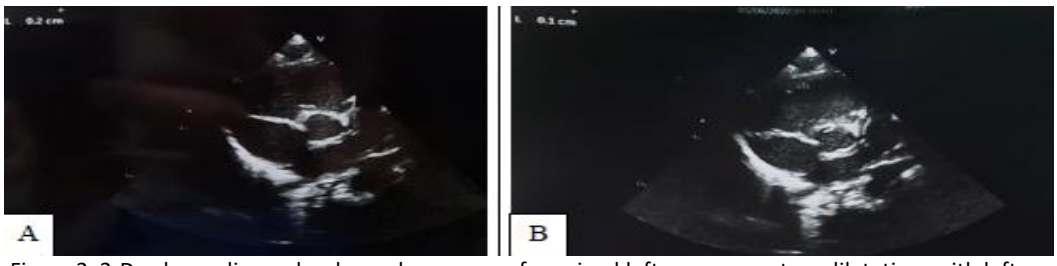


Figure 2. 2-D echocardiography showed presence of proximal left coronary artery dilatation, with left coronary artery measuring 0.20cm proximally (A) and 0.10cm distally (B).

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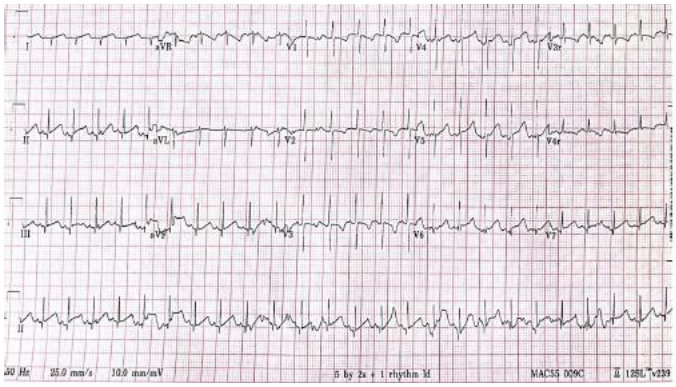

Figure 3. 15-Lead Electrocardiogram showed normal sinus rhythm and probable right ventricular hypertrophy.

Table 1. Laboratory Results

| Parameters | 1st HD | 2nd HD | 3rd HD | 4th HD | 5th HD |
|---|---|---|---|---|---|
| *CBC* | | | | | |
| Hgb*(g/dL)* | 10.2 (L) | 8.2 (L) | | | 11.6 (L) |
| Hct | 28 (L) | 22 (L) | | | 32 (L) |
| WBC*(10^9/L)* | 13.41 | 12.56 | | | 23.99 (H) |
| Neutrophil | 33 | 32 | | | 37 |
| Lymphocyte | 45 | 46 | | | 43 |
| Monocyte | 16 | 15 | | | 11 |
| Eosinophil | 7 | 7 | | | 8 |
| Basophil | 1 | - | | | 1 |
| Platelets *(10^12/L)* | 699 (H) | 648 (H) | | | 772 (H) |
| Reticulocyte count*(%)* | | 2.1 (1.1)* | | | |
| *Coomb's test* | | | | | |
| Direct | | | Negative | | |
| Indirect | | | Negative | | |
| *Electrolytes* | | | | | |
| Sodium*(mmol/L)* | 138 | | | | 135 |
| Potassium*(mmol/L)* | 5 | | | | 5.4 |
| Chloride*(mmol/L)* | 109 | | | | 111 |
| Calcium*(mmol/L)* | 2.51 | | | | 2.46 |
| *Inflammatory markers* | | | | | |
| CRP*(mg/L)* | 19.7 (3.9x↑) | | | | 2.1 |
| Procalcitonin*(ng/mL)* | | 0.21 | | | |
| LDH*(u/L)* | 243 | | | | |
| D-Dimer*(ng/mL)* | 1691.8 (3.3x↑) | | | | 656.4 (1.3x↑) |
| *Cardiac markers* | | | | | |
| CK-MB*(U/L)* | | 87 (3.5x↑) | | | 69 (2.8x↑) |
| ProBNP*(pg/mL)* | | 6781 (15x↑) | | | 1233 (2.7x↑) |
| Troponin I*(pg/mL)* | | 17.2 (↑risk) | | | 7.8 |
| *Kidney function* | | | | | |
| BUN*(mmol/L)* | | | | | 5.8 |
| Creatinine*(mg/dL)* | | | | | 0.33 |
| Urinalysis | Sp gr 1.005 Negative flow cytometry | | | | |
| Blood CS | Negative | | | | |
| Urine CS | ***Klebsiella Pneumoniae*** **10,000 colonies/ml** sensitive to Cefazolin, Ceftriaxone, Cefuroxime, Ciprofloxacin, Co-trimoxazole, Gentamicin, Nitrofurantoin, Piperacillin-tazobactam, resistant to Co-Amoxiclav | | | | |
| Peripheral blood smear | Normal white blood cell count with predominance of lymphocytes. Red blood cell count is decreased showing mostly normocytic, normochromic; few macrocytic, normochromic. Spherocytes (1+) and occasional elliptocytes are seen. Platelet count is increased. | | | | |
| COVID-19 RT PCR | Negative | | | | |

## DISCUSSION

The published literature regarding MIS-N is quite limited.[2-10] Majority of the reported cases presented with predominantly cardiac or respiratory involvement.[3-6,8-10] In the case series of Pawar, *et al.*, the gastrointestinal system was the third most common organ system involved in MIS-N, documented in 30% (6/20) of the neonates, after cardiac (90%, 18/20) and respiratory (55%, 11/20) systems.[9] Most of the reported cases of MIS-N were either symptomatic upon birth[3,4,6,8] or within the first week of life.[2,7,9,10] Our case shares some similarity with the MIS-N case reported by Kappanayil, *et al.* that described a late presenting term neonate who was initially born stable and fell suddenly ill on the 24th day of life.[5]

MIS-N was suspected in this neonate because of the mother's past history of COVID-19 infection seven weeks (34 weeks AOG) before the former developed fever. The diagnosis of MIS-N in our patient remains presumptive, made based on having a neonate with multi-organ dysfunction (cardiac, gastrointestinal, hematologic), following proven prenatal exposure to COVID-19, abnormal laboratory findings with dilated coronary artery on 2D echocardiography, elevated inflammatory markers and cardiac enzymes, and with a good response to immunomodulatory therapy. Neonatal Kawasaki Disease, with a high proportion of incomplete presentation in this age group, can be one plausible differential diagnosis to explain the coronary artery involvement, with anemia and thrombocytosis, which rapidly reversed with IVIG and corticosteroid therapy.[11] With the documented maternal COVID-19 during pregnancy and a prominent gastrointestinal manifestation, MIS-N was considered instead of neonatal Kawasaki disease.

By far, only three other cases of presumptive MIS-N were reported to have associated anemia.[6,8]

Shaiba, *et al.* described two preterms with presumptive MIS-N: a 36-weeker with anemia since birth, along with respiratory distress and cardiac involvement (moderately dilated left ventricle with poor systolic function, echogenic papillary muscles, widely patent ductus arteriosus with bidirectional shunt consistent with pulmonary hypertension, and elevated cardiac enzymes), and a 32-weeker with anemia on the 5th day of life, who also presented with respiratory symptoms upon birth, with elevated cardiac markers but normal 2D echo findings.[6] Malek, *et al.* reported a case of another late preterm (35-weeker) with presumptive MIS-N who likewise presented with respiratory distress and abnormal 2D echo findings (moderate persistent pulmonary hypertension, moderate perimembranous ventricular septal defect, small patent ductus arteriosus, and small atrial septal defect) upon birth, and was found with anemia on the 11th day of life. [8] Our patient had anemia on the 16th day of life, with feeding intolerance as the presenting symptom. The anemia worsened the next day without signs of overt bleeding.

Feeding intolerance has been reported in eight other cases.[2,3,9] Pawar, *et al.* described six neonates, of which two had brownish gastric aspirates, and two had lower gastrointestinal bleeding.[9] Aggrawal, *et al.* reported a 39-weeker who had nonbilious vomiting and abdominal distension on the 44th hour of life, along with respiratory symptoms and elevated cardiac markers, but normal 2D echo findings.[2] Borkotoky, *et al.* reported another term neonate (38-weeker) with the impression of persistent pulmonary hypertension upon birth, but who later (on the 14th day of life) presented with signs of early necrotizing enterocolitis with large aspirates pre-feed, increasing abdominal girth and vomiting.[3] Our patient presented with post-prandial vomiting on the first day of illness (16th day of life), with bilious OGT aspirate and findings of gas-dilated bowels with adynamic ileus in abdominal radiographs.

These gastrointestinal manifestations are more common in cases of multisystem inflammatory syndrome (MIS) compared to that of Kawasaki disease.

Ventricular dysfunction has been the most common 2-D echocardiographic finding in MIS-N reported in the literatures. [4-6,10] Our patient though had good left ventricular systolic and diastolic functions (EF 68% and FS 35%), but had proximal left coronary artery dilatation. Coronary artery dilatation or aneurysm was found in five other reported cases of presumed MIS-N.[4,7,9,10] In the case series of Pawar, *et al.*, all 20 neonates had cardiac involvement, with arrythmia as the most common cardiac abnormality found (44%, 11/20), followed by shock/cardiac dysfunction (20%, 5/10), and dilated coronaries were only found in two neonates (10%, 2/20).[9] Cardiac markers, when available, were all reported to be elevated.[2-6, 9-10] Our patient was found with highly elevated cardiac markers -- CK-MB, proBNP and Troponin I, upon work-up on the 17th day of life as soon as the impression of MIS-N was considered. ProBNP was 15 times elevated than normal prior to giving any medication.

To date, only a total of 33 cases of presumptive MIS-N were reported in the available literature (not including the *Possible* and *Unlikely MIS-N* cases from More, *et al.*). [2-10] Majority of the cases were managed with both IVIG and steroids with excellent response. [2-3,5-7,9-10] Our patient responded well to IVIG and steroids, with his clinical status and laboratory parameters remarkably improved thereafter.

To date, there is no clear, agreed case definition of MIS-N yet. Diagnostic criteria for MIS-N, as extrapolated from the CDC case definition for MIS-C, have been proposed (see Appendix A and B).[9,10] SARS-CoV-2 infection in newborns can be early-onset, secondary to vertical or intrapartum transmission, or late-onset, as acquired through close contact. [12-13]

Pawar, *et al.* differentiated MIS-N from MIS-C in neonates, defining MIS-N as multisystem inflammation in neonates secondary to maternal COVID-19 infection during pregnancy, thus involving two subjects (mother and neonate), while MIS-C in neonates refers to multisystem inflammation secondary to prior COVID-19 infection in the neonate, hence involving only one subject.[9] On the other hand, More, *et al.* identified MIS-N as multisystem inflammation in neonates with either maternal SARS-CoV-2 infection or previous neonatal SARS-CoV-2 infection.[10] In any case, our patient fulfilled these case definitions of MIS-N but most likely was due to maternal COVID-19 infection during pregnancy as our patient's RT-PCR for SARS-CoV2 was negative and he didn't have any symptoms of COVID-19 prior to this illness.

The exact etiopathogenesis of MIS-N is still being explored. Although vertical transmission of SARS-COV-2 infection has been reported in isolated cases, no conclusive evidence was found in a systematic review and meta-analysis of 39 studies involving 1316 women with SARS-COV-2 infection during pregnancy. [12,14-16] The limited expression of host membrane receptors for SARS-CoV-2 entry, namely angiotensin-converting enzyme (ACE) 2 and transmembrane protease serine 2 (TMPRSS2) in trophoblasts, was identified as a plausible reason to explain the low incidence of transplacental transmission of SARS-CoV-2 among term babies.[17] Efficient transplacental transfer of IgG antibodies has been well-documented.[18] These anti-spike IgG antibodies were speculated to be protective, similar to secretory IgA in breastmilk of COVID-19 vaccinated mothers, with no pathogenic role in MIS-N as they are not directed towards autoantigen.[9,19] Children though with MIS-C were found with elevated levels of antibodies against autoantigens (i.e., anti-SSB and anti-Jo-1).[19]

It is also postulated that autoantibodies against endothelial, gastrointestinal, and immune cells may have been produced in the maternal body after SARS-CoV-2 infection, and crossed the placenta to initiate MIS-N in genetically susceptible neonates, similar to how anti-SSA and anti-SSB cause rash and congenital heart block in neonates with neonatal lupus.[9] On the other hand, it is also speculated that the protective anti-spike IgG antibodies may cause autoimmune dysregulation in genetically susceptible newborns; these antibodies may bind to receptors on neutrophils and macrophages, leading to cytokine activation, which causes the various manifestations of MIS-N.[10]

There is lack of substantial evidence regarding the use of IVIG and corticosteroids in neonates, and its use in this age group has not yet been approved by the Food and Drug Administration (FDA). [2,4] Although available reports describing MIS-N have shown good clinical response to IVIG, with or without corticosteroids, the use of these drugs among neonates is not without risk; IVIG has been known to potentially cause necrotizing enterocolitis. [20] Immunomodulator therapy should be reserved for definitive cases, when indicated, to prevent overtreatment. In our patient, being symptomatic with laboratory abnormalities and maternal history of COVID-19, MIS-N was highly considered, thus the medical team decided to give IVIG and steroids. Luckily, our patient did not have any adverse events after medical treatments were given.

Since discharge, the baby remained stable and well, with consistent weight gain. Repeat 2D echo done upon follow up 2 months later showed normal findings with resolution of previously noted coronary artery dilatation. The baby was advised to continue exclusive breastfeeding, and to follow up for due vaccinations as well as regular paediatric well visits.

## CONCLUSION

We described a case of a previously well term neonate born to a mother who had COVID-19 at 34 weeks AOG, with sudden signs of bowel obstruction and eventual multisystem involvement (cardiac, gastrointestinal and hematologic). MIS-N was suspected in this neonate because of the mother's past history of COVID-19 infection seven weeks (34 weeks AOG) before the former developed fever. MIS-N is still evolving as a disease entity with no clear, directed guidance yet on diagnosis and management. A high index of suspicion for neonates of mothers with COVID-19 infection during pregnancy, and prompt diagnosis based on current available literatures, are keys to targeted management and better clinical outcomes. Additional case reports and series are warranted to increase awareness and enable better understanding of the disease pathology among clinicians for timely investigation, diagnosis and management of novel disease entities.

## FUNDING

This research received no external funding.

## CONFLICT OF INTEREST

None declared.

## INFORMED CONSENT STATEMENT

Informed consent was obtained from parents for the publication of the case.

## AUTHOR CONTRIBUTIONS

This case report was conceptualized by LADDI. CUC contributed to the literature search and manuscript preparation. LADDI, EVR, FVGV, RDG and JAR critically reviewed and edited the final manuscript.

All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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## APPENDIX A

**Proposed inclusion criteria for neonatal multisystem inflammatory syndrome (MIS-N) secondary to maternal SARS-CoV-2 exposure or infection by Pawar, *et al.* (2021)**

(1) A neonate aged <28 days at the time of presentation

(2) Laboratory or epidemiologic evidence of SARS-CoV-2 infection in the mother
- Positive SARS-CoV-2 testing by RT-PCR, serology (IgG or IgM), or antigen during pregnancy
- Symptoms consistent with SARS-CoV-2 infection during pregnancy
- Serological evidence (positive IgG specific to SARS-CoV-2 but not IgM) in the neonate

(3) Clinical criteria:
- Severe illness necessitating hospitalization AND
- Two or more organ systems affected [i.e., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological, temperature instability (fever or hypothermia)] OR
- Cardiac AV conduction abnormalities OR coronary dilation or aneurysms (without involvement of a second organ system)

(4) Laboratory evidence of inflammation
- One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-Dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin

(5) No alternative diagnosis (such as birth asphyxia-cord pH $\leq$ 7.0 and APGAR score $\leq$ 3 at 5 min; viral or bacterial sepsis-confirmed blood culture; maternal lupus resulting in neonatal AV conduction abnormalities; presence of these findings indicating an alternative diagnosis excludes MIS-N).

**APPENDIX B**

**Proposed inclusion criteria for neonatal multisystem inflammatory syndrome (MIS-N) by More, *et al.* (2022)**

(1) Symptoms presenting from birth to the first four weeks of life
(2) Fever along with two or more systems involvement (fever, if present, is suggestive but not mandatory for diagnosis in the newborn)
(3) Evidence of raised inflammatory markers such as CRP, PCT, D Dimer, Ferritin, and IL-6
(4) Evidence of SARS-CoV-2 antibodies in the neonate (considered mandatory for a diagnosis of MIS) and SARS-CoV-2 antigen should be negative during the presentation to rule out active SARS-CoV-2 infection to support the immunological process

AND

Associated evidence of maternal SARS-CoV-2 infection, defined as either supporting history or laboratory (positive SARS-CoV-2 quantitative RT-PCR test in a nasopharyngeal sample during the peripartum period) or epidemiological evidence of infection in the form of SARS-CoV-2 antibodies (for confirming the transplacental mechanism of MIS-N)

OR

History of prior confirmed neonatal SARS-CoV-2 infection (for confirming mechanism of MIS-N due autoantibodies secondary to SARS-CoV-2 infection) which can be classified based on the type of SARS-CoV-2 transmission in neonates as per WHO criteria as follows:

(a) In utero transmission — nasopharyngeal swab at age <24 hours positive for SARS-CoV-2 and positive serology for SARS-CoV-2 IgM and IgG.
(b) Intrapartum transmission — at least one test obtained at age <24 hours negative for SARS-CoV-2 with Negative serology (IgM or IgA) followed by positive RT-PCR at 24–48 hours or positive serology (IgM or IgA) at age 7–14 days that is corroborated by a positive serology test on a second sample obtained within 10 days of the first positive test.
(c) Postpartum transmission — at least one test obtained at age <48 hours was performed and negative for SARS-CoV-2 with Negative serology (IgM or IgA) at age <14 days followed by positive RT-PCR at age >48 hours OR positive serology (IgM or IgA) at age >14 days that is corroborated by a second positive serology test obtained within 10 days of the first positive test at age >14 days.

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 19-30 July-December 2022
Tuazon M, Delos Santos-Jamora MC, Florendo-Villanueva S and Panlilio-Runez R. Cancer and Chemotherapy in Pediatric COVID-19: A Case Series
https://doi.org/10.56964/pidspj20222302005

**CASE SERIES**

# CANCER AND CHEMOTHERAPY IN PEDIATRIC COVID-19: A CASE SERIES

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## ABSTRACT

**Objectives:** This case series aims to present three cases of pediatric cancer – two acute leukemia and one solid tumor with active COVID-19 infection who underwent chemotherapy

**Methodology:** Three cases of pediatric cancer who tested positive for SARS-CoV2 are presented. All proceeded with scheduled chemotherapy despite active COVID-19 infection. Two had no post-chemotherapy complications, while one had febrile neutropenia and hospital-acquired pneumonia.

**Results:** In this case series, COVID-19 infection in pediatric patients with cancer does not appear to be more severe compared with the general population. The severity of signs and symptoms can be attributed to a lower Cycle Threshold (CT) value and a co-infection. COVID-19 infection did not change the course and post-chemotherapy complications in all cases.

**Conclusion:** Patient demographics, comorbidities and type of malignancy played an essential role in the pre- and post-chemotherapy outcome. Individual patient factors including CT values, comorbidities, co-infections, COVID-19 disease severity classification, and blood count picture are also instrumental in the management and outcome of these cases. Pediatric cancer treatment should be a priority during active COVID-19 infection.

**KEYWORDS:** *COVID-19, Chemotherapy, Cancer, Children*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 19-30 July-December 2022
Tuazon M, Delos Santos-Jamora MC, Florendo-Villanueva S and Panlilio-Runez R. Cancer and Chemotherapy in Pediatric COVID-19: A Case Series
https://doi.org/10.56964/pidspj20222302005

## INTRODUCTION

The COVID-19 pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has quickly changed the course of medicine. Currently, more than 100 million people have been affected globally, with over 4 million deaths. In the Philippines alone, there are more than 1 million positive cases to date.[1] Fewer cases of COVID-19 have been reported in children (age 0-17 years) compared to adults with a milder course.[2] In recent studies, data on children with comorbidities, like cancer, and those with medical complexities, such as neurologic and metabolic conditions, showed that they were more likely to test positive for the disease.[3] Locally, the Surveillance and Analysis of COVID-19 in Children Nationwide (SALVACION) registry data showed that 7.4% of total pediatric COVID-19 positive patients are those with pediatric hematologic or oncologic disease. Additional data from the St. Jude Global registry for childhood cancer reported a total of 1,700 positive COVID-19 cases among pediatric patients from 49 countries across the globe.

During this pandemic, much attention was brought to delays in accessing timely pediatric care leading to unintended morbidity worldwide.[4] Delays in the diagnosis and treatment of life-threatening diseases, including cancer, have been reported. Intensive care admissions, which could have been prevented, were described due to delays in seeking medical attention. A lot of attention was directed to the implementation of basic guidelines to limit the spread of the virus but not enough focus was placed on the importance of adherence to pediatric cancer treatment and management. This poses a question on how to go about managing COVID-19 positive pediatric cancer patients.

In our institution, guidelines were developed for the treatment of cancer patients due to lack of international or local guidelines.

These cases can become the basis for developing recommendations that balance the risk of delaying chemotherapy during active COVID-19 infection. The risk of continuing chemotherapy despite disease severity especially during periods of immunosuppression can be further analyzed.

This case series presented 3 cases of children with hematologic and oncologic malignancies who underwent chemotherapy during active COVID-19 infection in a tertiary hospital. It highlighted differences in clinical presentation, course, diagnosis, management, and treatment outcomes. Distinctive features such as CT values, comorbidities, co-infections, COVID-19 disease severity classification, and blood count picture that played a role in the patients' overall outcome were emphasized. The importance of continuing pediatric cancer treatment despite active COVID-19 infection was stressed.

## PATIENT'S INFORMATION

A descriptive, observational study of three cases of pediatric cancer that underwent chemotherapy despite active COVID-19 infection are presented. An informed consent was obtained from all 3 cases regarding the write up of this case series.

### Case One

This is a case of a 2-year-old male, diagnosed with B-cell Acute Lymphoblastic Leukemia (ALL), Standard Risk since February 2021. Induction chemotherapy was started according to the Modified Societe Internationale D'oncologie Pediatrique (SIOP) Pediatric Oncology in Developing Countries (PODC) Graduated Intensity Regimen Low Income Country (LIC) 3 protocol. On his second week of treatment, he underwent mandatory SARS-CoV2 Reverse Transcription Polymerase Chain Reaction (RT-PCR) testing as per institutional protocol, which was positive. He had no known exposure and no other family member tested positive for COVID-19.

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He had no respiratory symptoms prior to, during, and after COVID-19 testing but had decreased appetite and generalized body weakness on review of systems. There was no blurring of vision, bleeding episodes, chest pain, constipation and or diarrhea, changes in urinary habits, vomiting, or seizures. He had pyomyositis of the right leg which presented with pain, limitation of range of motion, muscle tenderness and erythema of overlying skin and was on oral antibiotics prior to this admission. Routine blood tests revealed anemia and thrombocytopenia, which was addressed by transfusion of PRBC and platelet concentrate. Empiric antibiotics for pyomyositis were continued.

The absence of respiratory symptoms, normal routine chest radiograph, resolving pyomysositis, along with stable vital signs, despite a CT value of 33.38, prompted the managing team to pursue scheduled chemotherapy on the 6$^{th}$ day of his COVID-19 illness. He remained stable during and post-chemotherapy. Blood counts remained normal and he remained asymptomatic throughout his hospitalization. A repeat SARS-CoV2 RT-PCR taken 12 days from the 1st test (9$^{th}$ day of hospitalization) was negative and he was sent home and cleared for community integration.

Table 1. Diagnostic Profile and COVID-19 Status of Case One

| **SARS-CoV-2 Status (Pre-Chemotherapy)** | COVID-19 Asymptomatic |
|---|---|
| **Diagnostic Tests Pre-Chemotherapy** | |
| Hgb (g/dl) | 127 |
| WBC x $10^9$ /L | 2.60 |
| Neutrophils | 0.12 |
| Lymphocytes | 0.82 |
| Platelet Count x $10^9$/L | 75 |
| Absolute Neutrophil Count | 1003.1 |
| Chest Radiograph | Normal |
| CT-Value | FAM: 33.38<br>HEX: 34.15 |
| **SARS-CoV-2 Status (Post-Chemotherapy)** | COVID-19 Asymptomatic |
| **Diagnostic Tests Post-Chemotherapy** | |
| Hgb (g/dl) | 130 |
| WBC x $10^9$ /L | 2.83 |
| Neutrophils | 0.13 |
| Lymphocytes | 0.86 |
| Platelet Count x $10^9$/L | 50 |
| Absolute Neutrophil Count | 1003.7 |
| Chest Radiograph | Normal |
| **Complications Post-Chemotherapy** | None |
| **SARS-CoV-2 Status (on Discharge)** | Recovered |
| **SARS-CoV-2 Status (on Follow-up)** | No reinfection to date |

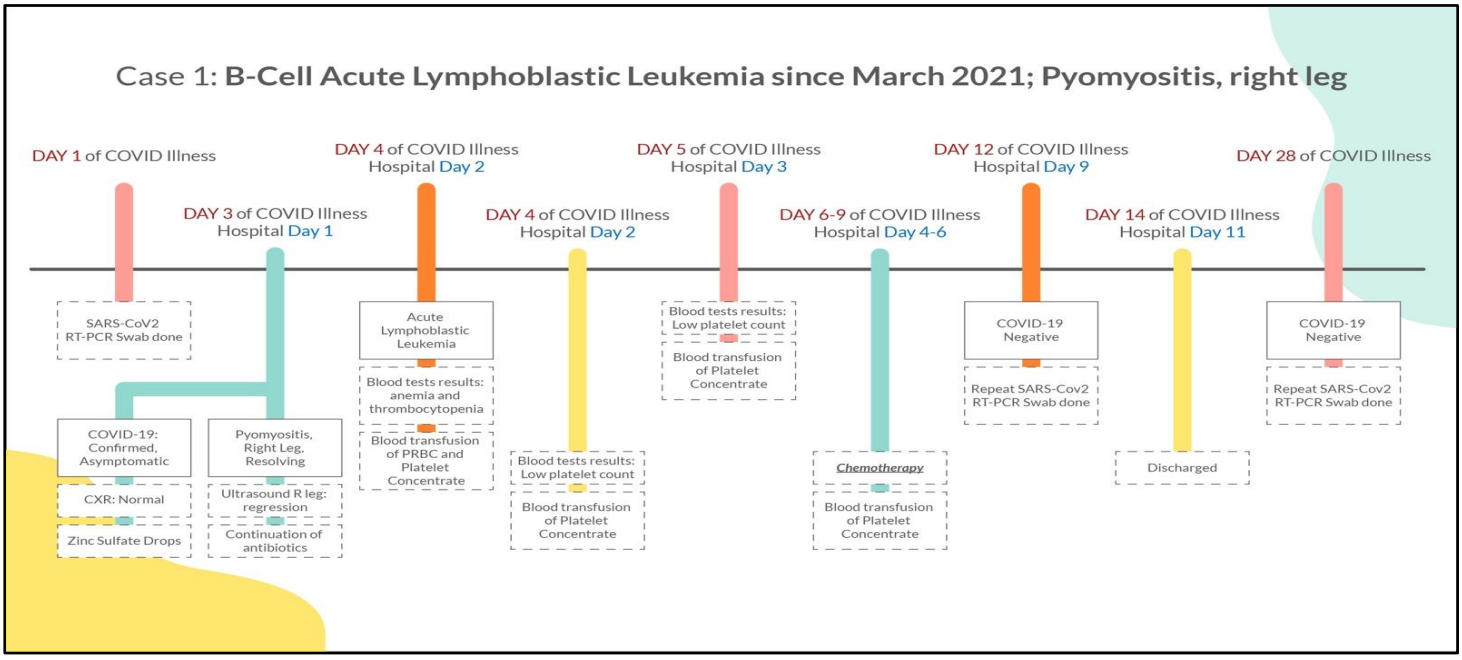


Figure 1. Timeline of Events and Course of Case One

**Case Two**

This is a case of a 3-year-old male diagnosed with B-cell Acute Lymphoblastic Leukemia, Standard Risk since April 2020. He was initiated on modified BFM/pre-B cell Children's Cancer Group (CCG) protocol and had his chemotherapy 2 weeks prior to this admission.

Five days prior to his scheduled fifth cycle of maintenance chemotherapy, he developed intermittent fever, with decreased appetite, oral intake, and activity which prompted consult at the Emergency Room. He had no known exposure to a COVID confirmed case; however, due to the presence of fever in this patient, and on following institutional protocols, SARS-CoV2 RT-PCR testing was done on admission.

On review of systems, he had generalized body weakness. There were no rashes, no blurring of vision, cough and colds, bleeding episodes, chest pain, changes in bowel and bladder habits, vomiting, or seizures. Physical examination showed that he had stable vital signs, with findings of pallor and non-tender lymphadenopathies on the occipital area. At that time, he had no respiratory findings and no retractions. His clinical signs and symptoms were attributed to a systemic viral infection (SVI) to consider dengue fever versus febrile neutropenia. His complete blood count revealed anemia, leukopenia, and thrombocytopenia. Dengue serology was positive for Immunoglobulin M (IgM) antibodies and negative for Immunoglobulin G (IgG). Dengue nonstructural protein 1 antigen (NS1) was also negative. He underwent mandatory SARS-CoV2 RT-PCR testing which revealed a positive result. The patient had no known exposures but his mother tested positive for COVID-19 as well.

Patient was started on empiric antibiotics for febrile neutropenia. In addition, platelet concentrate and PRBC transfusions were given. Serial CBC monitoring was continued and adequate hydration was maintained.

The improving trend of his blood picture, absence of respiratory symptoms, normal chest radiograph, and stable vital signs prompted the managing team to continue with his scheduled chemotherapy despite active COVID-19 with a low CT value (21.89) and the presence of dengue fever.

He had recurrence of febrile episodes two days post-chemotherapy and febrile neutropenia was again entertained. Work-up for sepsis was done revealing unremarkable results, but due to the low absolute neutrophil count (ANC), empiric antibiotics were continued. On the 12$^{th}$ hospital day, he had occasional dry cough with recurrence of intermittent fever and decreased appetite. Chest x-ray revealed pneumonia. Patient was managed as a case of healthcare-associated pneumonia and antibiotics were shifted to Piperacillin-Tazobactam.

On the 19th hospital day, he had worsening cough with fever despite antibiotic therapy. Repeat chest x-ray showed progression of pneumonia. Patient had persistently low ANC hence Fluconazole and Vancomycin were added to the treatment regimen. Gradual improvement was noted and on the 26$^{th}$ hospital day, 30 days after the onset of signs and symptoms, repeat RT-PCR test was negative. He was sent home improved on the 33$^{rd}$ hospital day. He remained COVID-19 negative on repeat SARS-CoV2 RT-PCR testing on follow-up, 41 days after his first COVID-19 diagnosis.

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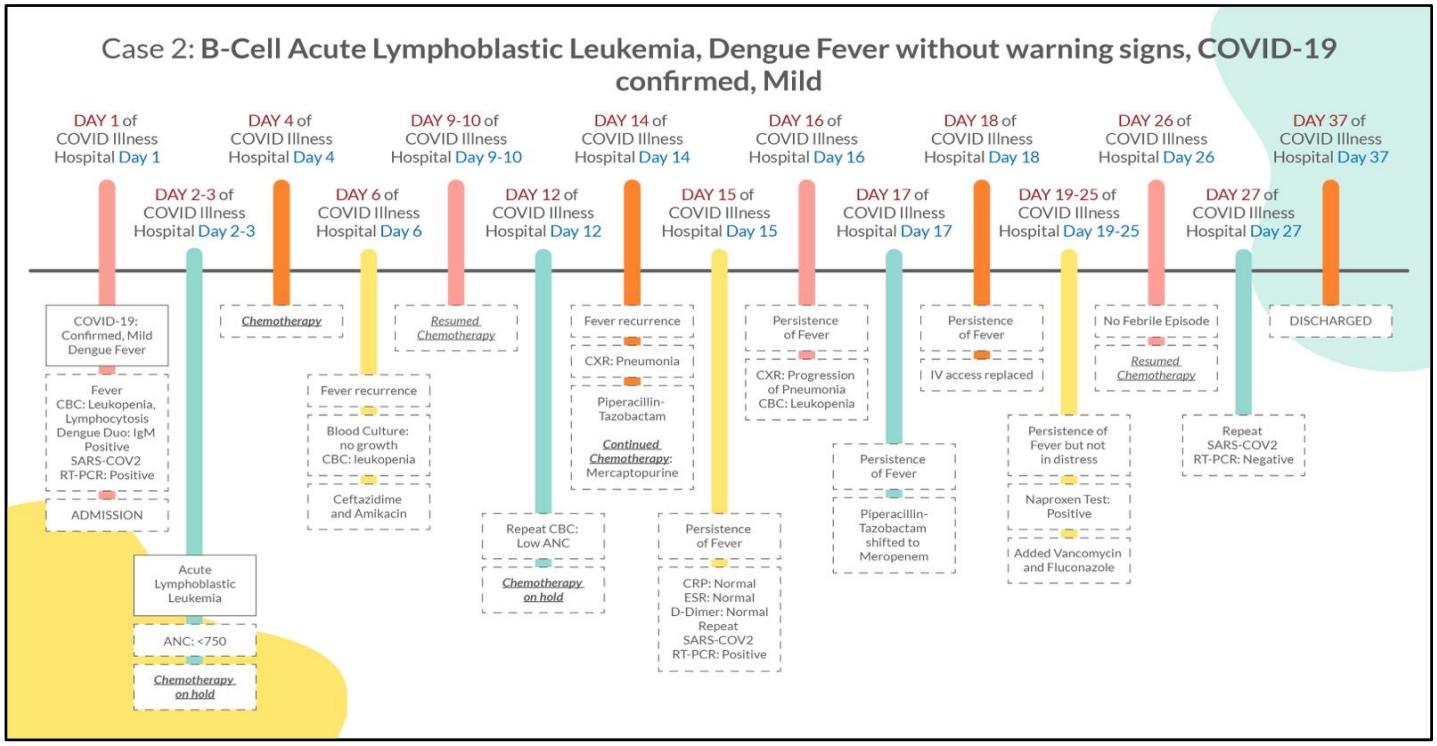


Figure 2. Timeline of Events and Course of Case Two

Table 2. Diagnostic Profile and COVID-19 Status of Case Two

| **SARS-CoV-2 Status (Pre-Chemotherapy)** | COVID-19 Mild |
|---|---|
| **Diagnostic Tests Pre-Chemotherapy** | |
| Hgb (g/dl) | 102 |
| WBC x $10^9$ /L | 1.27 |
| Neutrophils | 0.41 |
| Lymphocytes | 0.40 |
| Platelet Count x $10^9$/L | 374 |
| Absolute Neutrophil Count | 1005.1 |
| Chest Radiograph | Pneumonia |
| CT-Value | FAM: 21.89<br>ROX: 17.92 |
| **SARS-CoV-2 Status (Post-Chemotherapy)** | COVID-19 Moderate |
| **Diagnostic Tests Post-Chemotherapy** | |
| Hgb (g/dl) | 120 |
| WBC x $10^9$ /L | 2.59 |
| Neutrophils | 0.12 |
| Lymphocytes | 0.67 |
| Platelet Count x $10^9$/L | 274 |
| Absolute Neutrophil Count | 310.8 |
| Chest Radiograph | Pneumonia,<br>with progression |
| **Complications Post-Chemotherapy** | Febrile Neutropenia,<br>Healthcare-Associated Pneumonia |
| **SARS-CoV-2 Status (on Discharge)** | Recovered |
| **SARS-CoV-2 Status (on Follow-up)** | No reinfection to date |

## Case Three

This is case of a 7-year-old female diagnosed with Osteosarcoma of the right distal tibia last September 2020. She was started on European Osteosarcoma Intergroup (EOI) chemotherapy protocol in October of 2020 and is already on her 7$^{th}$ cycle, 2 weeks prior to this admission. She had above the knee amputation in December 2020 after four cycles of chemotherapy. She was also diagnosed with Pulmonary Tuberculosis (TB) in February 2020 and is on her 4$^{th}$ month of anti-TB therapy during this admission.

On her 8$^{th}$ cycle of maintenance chemotherapy, she underwent mandatory SARS-CoV2 RT-PCR testing per institutional protocol, which was positive. She was asymptomatic with no respiratory symptoms prior to, during, and after COVID-19 testing. She had no known exposures and no other family member had COVID-19 infection. On review of systems, there were no recent weight changes, anorexia, or growth delay and the rest of the organ systems were unremarkable. She had stable vital signs and physical examination was normal. Complete blood count was done with unremarkable results.

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The COVID-19 PCR had a high CT value of 23.17, but she was clinically stable with normal baseline laboratory results so the managing team proceeded with the scheduled chemotherapy. She remained asymptomatic post-chemotherapy with normal laboratory tests. She was able to complete the 5-day chemotherapy course without any complications. She was discharged and home isolation was continued for 5 more days. She remained asymptomatic on follow up 16 days after her COVID-19 infection.

Table 3. Diagnostic Profile and COVID-19 Status of Case Three

| **SARS-CoV-2 Status (Pre-Chemotherapy)** | COVID-19 Asymptomatic |
|---|---|
| **Diagnostic Tests Pre-Chemotherapy** | |
| Hgb (g/dl) | 119 |
| WBC x $10^9$ /L | 3 |
| Neutrophils | 0.50 |
| Lymphocytes | 0.39 |
| Platelet Count x $10^9$/L | 188 |
| Absolute Neutrophil Count | 1500 |
| Chest Radiograph | Normal |
| CT-Value | FAM: 23.17<br>ROX: 17.04 |
| **SARS-CoV-2 Status (Post-Chemotherapy)** | COVID-19 Asymptomatic |
| **Diagnostic Tests Post-Chemotherapy** | |
| Hgb (g/dl) | 110 |
| WBC x $10^9$ /L | 4.62 |
| Neutrophils | 0.86 |
| Lymphocytes | 0.12 |
| Platelet Count x $10^9$/L | 213 |
| Absolute Neutrophil Count | 3973.2 |
| Chest Radiograph | Normal |
| **Complications Post-Chemotherapy** | None |
| **SARS-CoV-2 Status (on Discharge)** | Home Isolation completed (recovered) |
| **SARS-CoV-2 Status (on Follow-up)** | No reinfection to date |

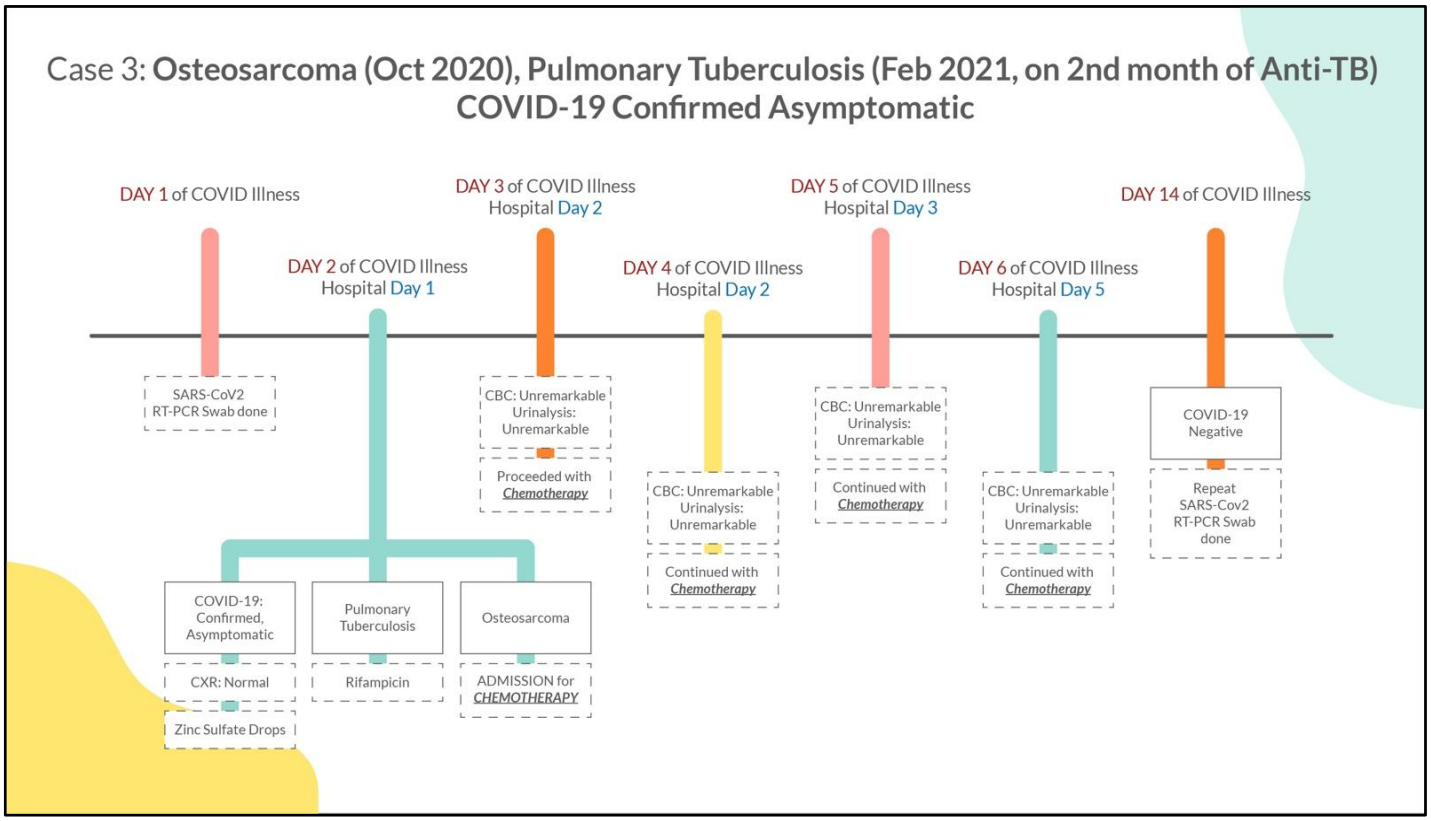


Figure 3. Timeline of Events and Course of Case Three

## DISCUSSION

Childhood cancer, although rare, is the second leading cause of death among children. Leukemia is the most common, representing about 28% of childhood cancers, closely followed by brain tumors, lymphomas, and bone cancers.[5] Locally, the Department of Health reports that 50% of all new cancers in children each year are leukemia (September 2020).[6] The Philippine Pediatric Society (PPS) Registry recorded 3,283 patients with ALL and 2,234 patients with osteosarcoma or bone and articular malignancy from 2015 to 2021.[7]

The incidence of COVID-19 among patients with cancer seems higher relative to the general population with the highest risk noted among those with hematologic and lung cancers.[8] Signs and symptoms of COVID-19 were reported to be mild in small surveys of children who developed COVID-19 while receiving immunosuppressive medications for kidney disease or inflammatory bowel disease.[9] In a study from a single institution in New York City, among 178 children with cancer, only 1 in 10 COVID-19 positive patients required admission for symptoms related to COVID-19.[10] Locally, in a tertiary hospital in Northern Luzon, of 207 children who tested positive for COVID-19, only 4.8% were children with malignancies. In this study, none of the 3 cases were admitted for symptoms related to COVID-19, and COVID-19 was just an incidental diagnosis during their admission. All three cases did not present with respiratory symptoms and only one presented with non-specific symptoms of fever and anorexia which could be attributed to COVID-19 and a concomitant dengue infection.

In a study by Westblade, *et al*. among 3,000 hospitalized patients with COVID-19, the viral load, measured through CT values, was highly predictive of morbidity and mortality in patients with or without cancer.[11]

Viral load on admission was an independent predictor of in-hospital mortality among patients with active cancer, with increasing viral load equating to increasing morbidity and mortality. A positive RT-PCR result may have variable CT levels from <24 to ≤32. Lower CT levels are associated with severe COVID-19 with complications and disease progression.[12,13] Cases 1 and 3 had asymptomatic COVID-19, with cycle threshold values of 33.58 and 23.17, respectively; while case 2 had a CT value of 21.89. A lower CT value correlates with a high viral load which could have accounted for his symptoms.

The Centers for Disease Control and Prevention (CDC) considers that cancer represents an established or potential risk for severe COVID-19.[14] However, not all data are consistent across studies.[15-17] Case 2 had a more progressive disease, initially presenting with fever (mild disease) later on evolving to moderate COVID-19 with fever and dry cough, crackles and chest x-ray findings of pneumonia. Case 1 and 3 had localized disease - pyomyositis on the right leg and pulmonary tuberculosis, respectively, and were asymptomatic throughout the COVID-19 illness.

Variations in clinical course may be attributed to the underlying characteristics of cancer populations in these studies, such as cancer type and chemotherapy protocol received. Other factors, including lower socioeconomic status, poorly controlled comorbidities, and older age are also associated with a worse prognosis, which influence mortality rates in patients with cancer and COVID-19.[18-20] Since comorbidities in all 3 cases were adequately addressed, this contributed to a milder course with better prognosis for all patients.

In limited studies conducted in countries like Europe and the US that touched on chemotherapy strategies, the population ranged from 2 to 18 years old (median of 12.8 years) with male predominance (70%).[22,23]

The most common underlying diagnosis was ALL (53%) and most had a newly diagnosed disease, with a minority having relapse/refractory cancer (75% vs. 25%). Majority had no reported comorbidities. The studies reported that approximately half (46%) of patients received mildly immunosuppressive chemotherapy, whereas 21% received moderately immunosuppressive treatment and 33% received severely immunosuppressive treatment. There appeared to be no correlation between COVID-19 severity with degree of chemotherapy-induced immuno-suppression. Only a minority of asymptomatic patients who underwent immunosuppressive treatment developed COVID-19 symptoms and most had mild illness.[22,23] In the 3 cases presented, all received immunosuppressive treatment during active COVID-19 infection and cases 1 and 3 remained to be classified as mild COVID-19. Only case 2 progressed from mild to moderate COVID-19 post chemotherapy which may be due to multiple factors, primarily his co-infections.

The reports registered in the Philippines reflect the global report, where 1-9 year old males are affected. ALL remains to be the most common diagnosis with ANC counts of >1000. Most are classified as asymptomatic or mild and most of them did not require hospitalization or treatment.[24] These data are comparable with the cases presented.

Lymphopenia has recurrently been discussed as a risk factor for severe disease in COVID-19 in adults. Kainth, *et al.* found a tendency for elevated total white blood cell counts in more severe pediatric cases, but not lymphopenia.[25] Additionally, in a systematic review of 7780 children with COVID-19, Hoang, *et al.* described an overall normal white blood cell count, with mild neutropenia and an elevated lymphocyte count.[26]

The development of lymphopenia in pediatric oncology patients may have implications for subsequent therapy, particularly immunotherapy. In some studies, COVID-19 positive cancer patients showed a reduced platelet count, but this was mostly ascribed as a chemotherapy-induced complication. Lymphopenia, C-Reactive Protein (CRP), and other lab parameters, such as LDH and ferritin, might support the diagnosis but might not predict the outcome of COVID-19 in cancer patients as they frequently have chemotherapy-induced cytopenias and acute phase reactants are frequently elevated.[27,28] Similarly, all 3 cases presented with leukopenia on admission while acute phase reactants were not obtained in this series.

A study by Jee, *et al.* disproved reports that suggested a high incidence of severe or critical illness (38.8%) in patients with cancer and COVID-19.[28] The study showed that patients treated with cytotoxic chemotherapy between 14 to 90 days before SARS-CoV-2 test positivity did not have an increased hazard ratio for the composite endpoint, ICU admission or death in separate analyses. This finding was further supported in a subgroup analysis and multiple sensitivity analyses that found no effect of chemotherapy on COVID-19-associated mortality in patients with cancer in various countries. All the three cases presented in this series were given chemotherapy within 14 days of active SARS-CoV-2 infection but none of them were admitted to the ICU and post-chemotherapy outcomes were favorable. In contrast, findings from China suggested worse outcomes with chemotherapy with severe COVID-19 as endpoint.

The pandemic paved the way for a rapid global response from the international childhood cancer community to provide rational solutions for problems in the care of children with cancer, regardless of where a child may live.

It is international consensus that, wherever possible, children presenting with a likely diagnosis of cancer during this pandemic undergo clinical assessment and appropriate investigations to establish a diagnosis and be offered effective therapy while mitigating the risk of exposure to COVID-19.[29-31] They further recommended that the standards of care for diagnosis, treatment, and supportive management not be compromised or electively modified during the pandemic, if at all possible. Lastly, all elements of cancer treatment should continue without modification unless resources become overwhelmed.

In pediatric patients with ALL, the major threat may be COVID-19-related interruption of treatment, or in some settings, treatment non-completion. The principal child cancer organizations (SIOP, SIOP-E, COG, SIOP-PODC, International Society of Paediatric Surgical Oncology (IPSO), Pediatric Radiation Oncology Society (PROS), International Children's Palliative Care Network (ICPCN) and St. Jude Global) recommend that children presenting with ALL undergo full investigation to establish diagnosis and risk stratification and commence treatment. They do not recommend any elective modification of maintenance chemotherapy, but in high COVID-19 prevalence regions, clinic visits should be minimized by extended dispensing of maintenance chemotherapy supported by virtual contact for clinical review. Supporting the family in this way may ensure treatment compliance and avoid treatment abandonment.

The Pediatric Hematology and Oncology Society of the Philippines has also sought the expertise of other societies outside the country on specific solutions to address our country's constantly changing health system. Suggestions include a separate COVID-19 in-patient facility for continued chemotherapy in most hospitals.

Patients should continue to receive chemotherapy in the COVID ward as per schedule and as clinically indicated.[32-35] It also includes screening for COVID-19 in patients prior to admission, outpatient chemotherapy, procedures requiring sedation, and screening in those who are symptomatic or have a history of travel and exposure. Imaging such as a chest x-ray or CT scan is done only to patients who develop respiratory symptoms or progresses to respiratory distress. Caregivers and those who accompany patients to the hospital are not required to undergo RT-PCR testing if they are asymptomatic, unless with history of exposure to COVID-19. Everyone should wear a mask before they enter the hospital and masking is mandatory throughout their hospital stay. Minimum health standards should be practiced at all times. COVID-19 positive pediatric cancer patients classified as mild and asymptomatic may have chemotherapy as scheduled as long as the management team waits until 5 to 7 days after symptom onset, provided no new symptoms appear. There was no need to modify chemotherapeutic dosing or use different treatment strategies based on intensity of chemotherapy since it was seen that some COVID-19 positive pediatric cancer patients shed the virus longer and remain RT-PCR positive for 4 to 6 weeks. Full dose chemotherapy was given with no problems but is not recommended if patient is symptomatic with respiratory symptoms.

Globally, due to problems and delays in cancer diagnosis and treatment, the medical team has been seeing more cancer patients with advanced disease. Because of travel restrictions, many people are reaching the hospital in advanced stages. Management guidelines and practical experience should be shared constantly among experts in the country.

In the tertiary hospital where these cases were reported, the scheduled chemotherapy continues provided that the following are present:

1) CT value is >25 if with mild symptoms related to COVID-19
2) CT value is >20 if with no symptoms related to COVID-19
3) ANC count is ≥1000 pre-chemotherapy

Overall, the general rule followed is that the benefits of cancer treatment should still outweigh the risks of chemotherapy.

## CONCLUSION

Demographics, comorbidities, and type of malignancy played an essential role in the pre- and post-chemotherapy outcomes of patients with cancer and COVID-19. Factors such as CT values, comorbidities, co-infections, COVID-19 classification on admission, and overall blood count picture are all instrumental in these cases' overall outcome. These variables helped predict COVID-19 risk and disease severity and became the basis for carrying on with their treatment. Altogether, it is noteworthy to maintain pediatric cancer treatment as a priority to avoid the harrowing effects and prevent children from becoming indirect victims of the COVID-19 pandemic due to disrupted therapies.

## FUNDING

This research received no external funding.

## CONFLICT OF INTEREST

None declared.

## INFORMED CONSENT STATEMENT

Informed consent was obtained from parents for the publication of the cases.

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Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 31-42 July-December 2022
Rivera AC, Pantig FMT, Maramba-Lazarte CC, Dy-Co AS, Rosales VOC, Sarmiento RFR, *et al.* SARS-CoV-2 Infection in Filipino Children: An Interim Report from the SALVACION Registry
https://doi.org/10.56964/pidspj20222302006

**ORIGINAL ARTICLE**

# SARS-CoV-2 INFECTION IN FILIPINO CHILDREN: AN INTERIM REPORT FROM THE SALVACION REGISTRY

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## ABSTRACT

**Background:** The COVID-19 pandemic continues to afflict nations worldwide. The Philippines is no exception which has recorded more than 3 million cases as of December 2021 with children comprising 12% of total cases. Since the start of the pandemic, the Pediatric Infectious Disease Society of the Philippines (PIDSP) has been collecting data nationwide, through an online pediatric COVID-19 registry (SALVACION registry), to provide a better understanding of COVID-19 in children in the local setting.

**Methods:** This was an ambispective cohort study of pediatric COVID-19 cases in the Philippines reported from March 2020 to December 2021. Data on clinical features, laboratory findings, disease severity, and treatment outcomes were voluntarily reported by physicians across the country. This study was approved by the Department of Health Single Joint Research Ethics Board.

**Results:** As of December 30, 2021, there were 2,127 cases reported in the registry, with a median age of 5 years (interquartile range: 1-13 years) and mostly mild (41.9%) or moderate (24.5%) in severity. The top symptoms reported were fever (57.9%), cough (42.7%), coryza/colds (29.4%), anorexia (25.2%), and difficulty of breathing (23.1%). The most common comorbidities were hematologic-oncologic diseases (7.4%), neurologic diseases (7.0%) and surgical conditions (4.4%), while the most common co-infections were sepsis (6.3%), dengue fever (4.8%) and healthcare-associated pneumonia (2.1%). Significantly higher median CRP, procalcitonin, D-dimer, ferritin, transaminases and lactate dehydrogenase were seen among severe/critical cases compared to non-severe cases. There was a high frequency of antibiotic use (58%). Most cases recovered, although 172 deaths were reported with an 8.6% case fatality rate. The most common comorbidities in those who died were neurologic (15.7%), cardiac (12.8%) and hematologic (11.6%) diseases.

**Conclusion:** Children across all age groups are susceptible to COVID-19 and most cases are mild or moderate in severity. Among severe and critical cases, the most common comorbidities were neurologic, hematologic-oncologic and cardiac diseases. Most patients recovered with supportive management.

**KEYWORDS:** *COVID-19, SARS-CoV-2, Child, Registry, Philippines, Pediatric Multisystem Inflammatory Disease*, *COVID-19 related*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and that all authors have met the requirements for authorship.

## INTRODUCTION

The novel Coronavirus disease 2019 (COVID-19) pandemic is a global health threat of unprecedented magnitude. Worldwide, as of April 19, 2022, there have been 503,131,834 reported cases and 6,200,571 deaths. The Western Pacific region has accounted for over 50 million cases, with about 20% reported in the pediatric population.[1]

SARS-CoV-2 causes an acute respiratory infection with varying severity across different age groups. The elderly and persons with comorbidities tend to have severe disease, while children are relatively spared.[2] There are, however, reports of severe to critical cases in the pediatric population with unusual manifestations described as Multisystem Inflammatory Syndrome in Children (MIS-C).

Infections in the younger age group is expected to increase due to the growing number of infections in adults and partly because younger children have challenges in practicing minimum public health standards. Although the true incidence of COVID-19 in children is unknown due to lack of widespread testing and priority in testing adults and those with severe illness, a systematic review by Ludvigsson showed that children have so far accounted for 1-5% of diagnosed COVID-19 cases with mild disease and fewer deaths. Fever and respiratory symptoms were prevalent among symptomatic children and only a few developed severe pneumonia with elevated inflammatory markers.[4] Another review by Zimmermann showed that 83% of children with COVID-19 had a positive contact history, with a mean incubation period of 7 days. Co-infections were reported in up to 79% of children (mainly with *Mycoplasma sp.* and influenza), and up to 35% were asymptomatic.[5] An epidemiological study of pediatric COVID-19 infection across Asia demonstrated that risk factors for severe disease were age younger than 12 months, presence of comorbidities and cough at presentation, with an overall mortality of 2.3%.[6]

In several epidemiological studies of this disease, the pediatric population seems underrepresented with low death rates. A multicenter study in Europe involving 582 children in 25 countries described a case fatality rate of 0.69%.[3]

As of May 13, 2022, the Philippines has reported 3,687,748 COVID-19 cases, with the pediatric age group (less than 19 years old) accounting for 12% of cases.[7] To date, there is no published data on the epidemiology of COVID-19 in the Filipino pediatric population. Blasurca, *et al.* published a case series of 5 pediatric patients with MIS-C[8] and a case report of fulminant hepatitis secondary to SARS-CoV-2.[9] These reports of severe manifestations of COVID-19 in children are probably outliers in the more than 150,000 cases of COVID-19 in children in the Philippines. A local study by Po, *et al.* also looked into the outcomes of infants born to mothers with SARS-CoV-2 infection, and it showed that none of the infants had COVID-19.[10] With the scarcity of data on pediatric COVID-19 in the Philippines, the Pediatric Infectious Disease Society of the Philippines created an online registry for the surveillance and analysis of COVID-19 in children nationwide (SALVACION Registry). This study aimed to look into the clinical profile of COVID-19 among Filipino children and describe the diagnostic and therapeutic management in the pediatric population.

## MATERIALS AND METHODS

This is an ambispective cohort study of patients 0 to 18 years old diagnosed with COVID-19 in the Philippines and reported to the SALVACION Registry from March 2020 to December 31, 2021. The SALVACION Registry is a web-based pediatric COVID-19 registry developed by the UP-NIH National Telehealth Center in collaboration with the SALVACION Team of PIDSP and supported by the Philippine Pediatric Society (PPS).

Physicians from both government and private institutions voluntarily uploaded to the SALVACION registry website the data of their pediatric patients with probable or confirmed COVID-19 admitted in the hospital or seen at their respective outpatient departments.

The following data were submitted: reporting institution, demographic information, exposure history, comorbidities, co-infections, clinical presentation, laboratory and imaging results, treatment regimen and outcome. Neither identity nor personal data were collected for the study.

Classification of patients as confirmed or probable COVID-19 was based on the definitions provided in the PPS-PIDSP Interim Guidelines on the Screening, Assessment and Clinical Management of Pediatric Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) Version 4, February 6, 2021 published in the PIDSP Journal. Cases were classified as "non-severe" if they presented with mild or moderate features based on the guideline, and "severe" if they presented with severe and critical features.

This study adhered to the ethical considerations and principles set out in relevant guidelines, including the Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, and National Ethics Guidelines for Health Research. The study was reviewed and approved by the DOH Single Joint Research Ethics Board (SJREB-2020-40).

### Data Analysis

Descriptive statistics were used for categorical variables and expressed as frequencies and percentages. Shapiro-Wilk test was used to determine the normality assumption of continuous variables. Continuous quantitative data that met normality assumptions were summarized using mean and standard deviation (SD), while those that did not were described using median and range.

An independent t-test was used to compare means between severe and non-severe pediatric cases for continuous variables.

The Mann-Whitney U test was used if the data were not normally distributed. For categorical variables, the chi-square test was used to compare the outcomes. Missing variables were neither replaced nor estimated. The null hypothesis was rejected at a 0.05 α-level of significance. STATA 15.0 was used for data analysis.

## RESULTS

The registry collected 2,127 pediatric cases of COVID-19 from March 2020 to December 2021.

The median age of patients was 5 years (interquartile range: 1-13 years). Most cases were in the 1 to 5-year age group (26.2%), followed by the 11 to 15-year age group (20.8%). Males comprised 57.12% of cases. As to disease severity, patients were predominantly classified as mild (41.9%) and moderate (24.5%). There were 363 (17.1%) asymptomatic cases and 16 (0.7%) with MIS-C. Of the reported patients, 89.5% were hospitalized. There were 62 reports which were excluded (unverified age and unknown severity), resulting in 2,065 patients for this study (Table 1).

Table 1. Demographic and clinical characteristics of confirmed COVID-19 pediatric patients in the SALVACION registry *(n = 2,065)*

| Parameter | | Frequency (%) |
|---|---|---|
| **Age** | Unknown/Unverified | 52 (2.44) |
| | 0-30 days old | 174 (8.18) |
| | 1 mo - <1 yr | 318 (14.95) |
| | 1 – 5 yr | 558 (26.23) |
| | 6 – 10 yr | 342 (16.08) |
| | 11 – 15 yr | 442 (20.78) |
| | 16 – 18 yr | 241 (11.33) |
| **Sex** | Unknown/Unverified | 3 (0.14) |
| | Male | 1215 (57.12) |
| | Female | 909 (42.74) |
| **Severity** | Unknown/Unverified | 10 (0.47) |
| | Asymptomatic | 363 (17.07) |
| | Mild | 892 (41.94) |
| | Moderate | 521 (24.49) |
| | Severe | 169 (7.95) |
| | Critical | 156 (7.33) |
| | MIS-C | 16 (0.75) |
| **Admission Status** | Hospitalized | 1904 (89.52) |
| | Not hospitalized | 223 (10.48) |

Children below 1 year of age comprised 33.13% and 41.06% of those with severe and critical diseases, respectively. All cases of MIS-C were between 1 to 15 years old, with most cases in the 6 to 10-year age group (43.7%). The most common pre-existing conditions reported were hematologic-oncologic diseases (7.4%), neurologic diseases (7.0%) and surgical conditions (4.4%). Among severe and critical cases, the most common comorbidities were neurologic diseases (14.5% and 14.6%), hematologic-oncologic diseases (11.4% and 7.9%) and cardiac diseases (9.0% and 8.6%).

Among children with MIS-C, pre-existing conditions identified were obesity (n=3), acute appendicitis (n=1) and concomitant intestinal amoebiasis (n=1) (Table 2).

Top symptoms reported were fever (57.9%), cough (42.7%), coryza/colds (29.4%), anorexia (25.2%) and difficulty of breathing (23.1%) which was also the most common symptom among severe and critical patients (69%). The most common co-infections were sepsis (6.3%), dengue fever (4.8%), healthcare-associated pneumonia (2.1%) and tuberculosis (1.5%) (Table 2).

Table 2. Clinical characteristics according to disease severity

| Parameter | | Total (n=2065) | Asymp-tomatic (n=353) | Mild (n=872) | Moderate (n=507) | Severe (n=166) | Critical (n=151) | MIS-C (n=16) |
|---|---|---|---|---|---|---|---|---|
| | | Frequency (%) | | | | | | |
| **Age** | <30 days | 172 (8.33) | 50 (14.16) | 29 (3.33) | 51 (10.06) | 18 (10.84) | 24 (15.89) | 0 |
| | 1 – 11 months | 316 (15.3) | 37 (10.48) | 96 (11.01) | 108 (21.3) | 37 (22.29) | 38 (25.17) | 0 |
| | 1 – 5 years | 556 (26.92) | 83 (23.51) | 252 (28.9) | 145 (28.6) | 32 (19.28) | 40 (26.49) | 4 (25.0) |
| | 6 – 10 years | 340 (16.46) | 58 (16.43) | 165 (18.92) | 67 (13.21) | 28 (16.87) | 15 (9.93) | 7 (43.75) |
| | 11 – 15 years | 441 (21.36) | 72 (20.4) | 223 (25.57) | 87 (17.16) | 30 (18.07) | 24 (15.89) | 5 (31.25) |
| | 16 – 18 years | 240 (11.62) | 53 (15.01) | 107 (12.27) | 49 (9.66) | 21 (12.65) | 10 (6.62) | 0 |
| **Pre-existing conditions** | Obesity | 68 (3.29) | 4 (1.13) | 13 (1.49) | 25 (4.93) | 19 (11.45) | 4 (2.65) | 3 (18.75) |
| | Bronchial asthma | 54 (2.62) | 3 (0.85) | 23 (2.64) | 17 (3.35) | 7 (4.22) | 4 (2.65) | 0 |
| | Tuberculosis | 31 (1.50) | 2 (0.57) | 8 (0.92) | 12 (2.37) | 5 (3.01) | 4 (2.65) | 0 |
| | Other respiratory conditions | 27 (1.31) | 2 (0.85) | 2 (0.46) | 4 (0.99) | 10 (6.02) | 11 (7.28) | 0 |
| | Cardiac disease | 77 (3.73) | 5 (1.42) | 17 (1.95) | 27 (5.33) | 15 (9.04) | 13 (8.61) | 0 |
| | Hematologic disease | 152 (7.36) | 23 (6.52) | 61 (7) | 37 (7.3) | 19 (11.45) | 12 (7.95) | 0 |
| | Kidney disease | 63 (3.05) | 8 (2.27) | 16 (1.83) | 21 (4.14) | 11 (6.63) | 7 (4.64) | 0 |
| | Neurologic disease | 145 (7.02) | 14 (3.97) | 41 (4.82) | 45 (8.88) | 23 (14.46) | 22 (14.57) | 0 |
| | Prematurity | 44 (2.13) | 2 (0.57) | 4 (0.46) | 14 (2.76) | 11 (6.63) | 13 (8.61) | 0 |
| | Pregnancy | 12 (0.58) | 2 (0.57) | 3 (0.34) | 4 (0.79) | 1 (0.6) | 2 (1.32) | 0 |
| | Smoking | 4 (0.19) | 0 | 2 (0.23) | 0 | 2 (1.2) | 0 | 0 |
| | Gastrointestinal disorders | 34 (1.65) | 5 (1.42) | 16 (1.83) | 5 (0.99) | 3 (1.81) | 5 (3.31) | 1 (6.25) |
| | Surgical GI conditions | 91 (4.41) | 30 (8.5) | 33 (3.78) | 19 (3.75) | 4 (2.41) | 4 (2.65) | 1 (6.25) |
| | Genetic/Metabolic | 32 (1.55) | 2 (0.57) | 12 (1.26) | 7 (1.38) | 4 (1.81) | 7 (4.64) | 0 |
| | Endocrinologic | 16 (0.77) | 3 (0.85) | 6 (0.69) | 2 (0.39) | 4 (2.41) | 1 (0.66) | 0 |
| | Rheumatologic | 10 (0.48) | 2 (0.57) | 4 (0.46) | 2 (0.39) | 2 (1.2) | 0 | 0 |
| | Allergic disease | 18 (0.87) | 0 | 10 (0.92) | 6 (1.18) | 2 (1.2) | 0 | 0 |
| | Immunodeficiency | 3 (0.15) | 1 (0.28) | 1 (0.11) | 0 | 1 (0.6) | 0 | 0 |
| | Psychiatric | 2 (0.1) | 1 (0.28) | 0 | 1 (0.2) | 0 | 0 | 0 |
| | Malnutrition | 19 (0.92) | 1 (0.28) | 7 (0.8) | 6 (1.18) | 3 (1.81) | 2 (1.32) | 0 |
| **Symptoms** | Fever | 992 (57.94) | - | 472 (54.13) | 312 (61.54) | 113 (68.07) | 79 (52.32) | 16 (100) |
| | Cough | 731 (42.70) | - | 303 (34.75) | 261 (51.48) | 98 (59.04) | 66 (43.71) | 3 (18.75) |

| Parameter | | Total (n=2065) | Asymp-tomatic (n=353) | Mild (n=872) | Moderate (n=507) | Severe (n=166) | Critical (n=151) | MIS-C (n=16) |
|---|---|---|---|---|---|---|---|---|
| | | Frequency (%) | | | | | | |
| **Symptoms (cont.)** | Coryza/Colds | 503 (29.38) | - | 268 (30.73) | 153 (30.18) | 52 (31.33) | 28 (18.54) | 2 (12.5) |
| | Difficulty of breathing | 396 (23.13) | - | 36 (4.13) | 136 (26.82) | 114 (68.67) | 105 (69.54) | 5 (31.25) |
| | Sore throat | 118 (6.89) | - | 74 (8.49) | 26 (5.13) | 11 (6.63) | 5 (3.31) | 2 (12.5) |
| | Watery stools | 250 (14.60) | - | 121 (13.88) | 84 (16.57) | 22 (13.25) | 15 (9.93) | 8 (50) |
| | Vomiting | 322 (18.81) | - | 172 (19.72) | 94 (18.54) | 26 (15.66) | 21 (13.91) | 9 (56.25) |
| | Poor suck/decreased appetite | 431 (25.18) | - | 130 (14.91) | 146 (28.8) | 68 (40.96) | 75 (49.67) | 12 (75) |
| | Seizure | 152 (8.88) | - | 49 (5.62) | 59 (11.64) | 19 (11.45) | 24 (15.89) | 1 (6.25) |
| | Muscle pain | 90 (5.26) | - | 52 (5.96) | 19 (3.75) | 11 (6.63) | 5 (3.31) | 3 (18.75) |
| | Loss of smell | 71 (4.15) | - | 50 (5.73) | 19 (3.75) | 2 (1.2) | 0 | 0 |
| | Loss of taste | 54 (3.15) | - | 35 (4.01) | 17 (3.35) | 1 (0.6) | 1 (0.66) | 0 |
| | Abdominal pain | 242 (14.14) | - | 123 (14.11) | 70 (13.81) | 23 (13.86) | 18 (11.92) | 8 (50) |
| | Headache | 52 (3.04) | - | 34 (3.9) | 10 (1.97) | 5 (3.01) | 2 (1.32) | 1 (6.25) |
| | Rash | 37 (2.16) | - | 18 (2.06) | 11 (2.17) | 1 (0.6) | 0 | 7 (43.75) |
| | Oral and conjunctival mucosal changes | 13 (0.76) | - | 4 (0.46) | 4 (0.79) | 0 | 0 | 5 (31.25) |
| | Chest pain | 12 (0.70) | - | 4 (0.46) | 5 (0.99) | 2 (1.2) | 1 (0.66) | 0 |
| | Epistaxis | 12 (0.70) | - | 6 (0.69) | 3 (0.59) | 3 (1.81) | 0 | 0 |
| **Concurrent Infections** | Influenza | 7 (0.34) | 0 | 6 (0.69) | 0 | 1 (0.6) | 0 | 0 |
| | Dengue fever | 99 (4.79) | 2 (0.57) | 56 (6.42) | 24 (4.73) | 12 (7.23) | 5 (3.31) | 0 |
| | Tuberculosis | 31 (1.50) | 2 (0.57) | 8 (0.92) | 12 (2.37) | 5 (3.01) | 4 (2.65) | 0 |
| | Healthcare-associated pneumonia | 44 (2.13) | 3 (0.85) | 9 (1.03) | 5 (0.99) | 15 (9.04) | 12 (7.95) | 0 |
| | Sepsis | 130 (6.30) | 8 (2.27) | 20 (2.29) | 41 (8.09) | 27 (16.27) | 34 (22.52) | 0 |
| | Bacterial Meningitis | 13 (0.63) | 0 | 4 (0.46) | 6 (1.18) | 0 | 3 (1.99) | 0 |
| | Urinary tract infection | 28 (1.36) | 2 (0.57) | 16 (1.83) | 6 (1.18) | 2 (1.2) | 2 (1.32) | 0 |
| | Gastrointestinal infections | 13 (0.63) | 1 (0.28) | 6 (0.69) | 4 (0.79) | 1 (0.6) | 0 | 1 (6.25) |
| | Skin, soft tissue, musculoskeletal infections | 15 (0.73) | 2 (0.57) | 6 (0.69) | 5 (0.99) | 1 (0.6) | 1 (0.66) | 0 |
| | Viral exanthem | 3 (0.15) | 0 | 3 (0.34) | 0 | 0 | 0 | 0 |
| | Leptospirosis | 3 (0.15) | 0 | 0 | 2 (0.39) | 1 (0.6) | 0 | 0 |

Table 3 shows the laboratory findings of cases in the registry. There were significantly higher median CRP, procalcitonin, D-dimer, ferritin, transaminases and lactate dehydrogenase among severe/critical cases compared to non-severe cases.

Features of pneumonia were radiologically seen in 52.37% of cases. Among those with abnormal chest CT scan findings, bilateral peripheral ground glass opacities were the most commonly seen (48.72%).

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https://doi.org/10.56964/pidspj20222302006

Table 3. Laboratory findings according to disease severity

| Parameter | | Total (n=2065) | Non-severe (n=1732) | Severe/Critical (n=317) | MIS-C (n=16) | *p value* |
|---|---|---|---|---|---|---|
| | | Median (Range) | | | | |
| **Complete blood count** | Hemoglobin | [N=1772] 127 (17-269) | [N=1462] 128 (22-265) | [N=294] 120 (17-269) | [N=16] 119.5 (84-148) | <.001 |
| | Hematocrit | [N=1772] 0.38 (0.02-0.81) | [N=1462] 0.38 (0.02-0.8) | [N=294] 0.36 (0.07-0.81) | [N=16] 0.34 (0.24-0.43) | <.001 |
| | WBC | [N=1773] 9.16 (0.1-99.99) | [N=1463] 8.82 (0.1-99.99) | [N=294] 11.15 (0.1-99.99) | [N=16] 12 (4.72-27) | <.001 |
| | Segmented neutrophil | [N=1757] 0.56 (0.01-0.99) | [N=1454] 0.54 (0.01-0.99) | [N=288] 0.61 (0.01-0.96) | [N=15] 0.85 (0.44-0.95) | <.001 |
| | Lymphocyte count | [N=1758] 0.34 (0.01-0.93) | [N=1454] 0.35 (0.01-0.93) | [N=289] 0.3 (0.01-0.91) | [N=15] 0.09 (0.01-0.45) | <.001 |
| | Platelet | [N=1082] 300 (2-2745) | [N=890] 308 (5-2745) | [N=184] 255 (2-844) | [N=8] 181 (117-667) | <.001 |
| **Others** | CRP | [N=799] 6 (0.02-576) | [N=623] 5 (0.02-576) | [N=160] 12 (0.1-292) | [N=16] 107 (6-508) | <.001 |
| | Procalcitonin | [N=515] 0.28 (0.01-248) | [N=375] 0.16 (0.01-200) | [N=128] 1 (0.05-248) | [N=12] 16.165 (0.11-118.05) | <.001 |
| | ESR | [N=184] 23.5 (0.03-289.22) | [N=143] 19 (0.03-289.22) | [N=30] 34.5 (2-135) | [N=11] 40 (7-110) | .319 |
| | D-dimer | [N=157] 1.2 (0.1-22.51) | [N=73] 0.95 (0.1-17.31) | [N=79] 1.64 (0.12-22.51) | [N=5] 2.4 (1.87-10) | .024 |
| | Ferritin | [N=233] 298 (1.63-30713) | [N=124] 176.5 (1.63-28058) | [N=100] 511.5 (7.8-30713) | [N=9] 712 (405-2907) | .088 |
| | Aspartate aminotransferase | [N=233] 53.5 (1.07-5147.44) | [N=91] 37.5 (1.07-667.7) | [N=135] 73 (2-5147.44) | [N=7] 49 (14.1-125) | .002 |
| | Alanine aminotransferase | [N=251] 37 (1.1-2919) | [N=99] 27 (1.1-334.3) | [N=145] 43 (1.64-2919) | [N=7] 53 (16.6-167) | .007 |
| | Lactate dehydrogenase | [N=206] 436.5 (7.55-10483) | [N=118] 365.62 (7.55-5564) | [N=82] 617 (78-10483) | [N=6] 345.45 (282-507) | <.001 |
| | Creatine kinase | [N=80] 53.7 (0.15-11397) | [N=31] 30.29 (0.15-1528) | [N=47] 68 (4.7-11397) | [N=2] 21.5 (15-28) | .073 |
| | IL-6 | [N=77] 111 (1.99-4325) | [N=24] 91.5 (2-1296) | [N=53] 120 (1.99-4325) | - | .225 |
| | Troponin I ng/ml | 0.0275 (0.007-1.8) | [N=2] 0.0275 (0.025-0.03) | [N=2] 0.9035 (0.007-1.8) | - | |
| | Pro-BNP pg/ml | 89.76 (34.71-5,352) | 86.1 | [N=2] 834.88 (89.76-1580) | - | |
| | CK-MB U/L | 72.6 (14.5-150) | [N=4] 47.495 (14.5-72.6) | 134 (108.8-150) | - | |
| **CXR findings** | Normal X-ray findings | 804 (47.63) | 741 (53.73) | 58 (19.8) | 5 (31.25) | |
| | Abnormal X-ray findings | 884 (52.37) | 638 (46.27) | 235 (80.2) | 11 (68.75) | |

| Parameter | | Total (n=2065) | Non-severe (n=1732) | Severe/Critical (n=317) | MIS-C (n=16) | *p value* |
|---|---|---|---|---|---|---|
| | | Median (Range) | | | | |
| CXR findings (cont.) | No infiltrates | 21 (2.38) | 20 (3.13) | 1 (0.43) | 0 (0) | |
| | Localized infiltrates | 386 (43.67) | 301 (47.18) | 78 (33.19) | 7 (63.64) | |
| | Multilobar infiltrates | 312 (35.29) | 192 (30.09) | 117 (49.79) | 3 (27.27) | |
| | Pleural effusion | 69 (7.81) | 35 (5.49) | 32 (13.62) | 2 (18.18) | |
| | Others | 199 (22.51) | 142 (22.26) | 53 (22.55) | 4 (36.36) | |
| Chest CT scan findings | Normal chest CT scan findings | 7 (8.24) | 4 (9.76) | 3 (6.98) | 0 (0) | |
| | Abnormal chest CT scan findings | 78 (91.76) | 37 (90.24) | 40 (93.02) | 1 (100) | |
| | Bilateral peripheral ground-glass opacities | 38 (48.72) | 18 (48.65) | 19 (47.5) | 1 (100) | |
| | Unilateral peripheral ground-glass opacities | 5 (6.41) | 3 (8.11) | 2 (5) | 0 (0) | |
| | Multifocal or diffuse ground-glass opacities | 12 (15.38) | 5 (13.51) | 7 (17.5) | 0 (0) | |
| | Segmental or lobar consolidation | 20 (25.64) | 6 (16.22) | 14 (35) | 0 (0) | |
| | Pleural effusion | 19 (24.36) | 9 (24.32) | 9 (22.5) | 1 (100) | |
| | Others | 25 (32.05) | 11 (29.73) | 14 (35) | 0 (0) | |
| Chest Ultrasound findings | Abscess | 0 | 0 | 0 | 0 | |
| | Effusion | 10 (83.33) | 5 (100) | 5 (71.43) | 0 | |
| | Others | 3 (25) | 0 | 3 (42.86) | 0 | |
| 2D Echocardiography findings [N=5] | Myocardial dysfunction | - | - | - | 2 (40) | - |
| | Coronary arteritis | - | - | - | 1 (20) | - |
| | Pericardial effusion | - | - | - | 3 (60) | - |
| ABG | pH | [N=189] 7.39 (6.9-7.62) | [N=44] 7.425 (7.22-7.62) | [N=143] 7.37 (6.9-7.6) | [N=2] 7.335 (7.27-7.4) | |
| | PaCO2 | [N=188] 28.75 (9.4-99) | [N=44] 28 (10-50.5) | [N=142] 29 (9.4-99) | [N=2] 23.5 (23-24) | |
| | HCO3 | [N=188] 18.2 (1.9-49) | [N=44] 18.8 (4.1-38) | [N=142] 18.05 (1.9-49) | [N=2] 15.75 (14-17.5) | |
| | PaO2 | [N=188] 117.3 (18.8-345) | [N=44] 99 (18.8-345) | [N=142] 124 (21-327) | [N=2] 164.5 (126-203) | |

Table 4 shows the treatment and outcomes of patients. Antibiotics were the most commonly used drugs, with 58% of patients receiving at least one type of antibiotic. Nutritional support with zinc sulfate (57.2%) and vitamin D (39.9%) were also commonly used. Among antivirals, remdesivir was used in 3.15% of patients. The frequency of corticosteroid use was 11%.

Most severe and critical COVID-19 patients were given antibiotics (94.32%), corticosteroids (38.17%) with dexamethasone being the most commonly used (80.99%), remdesivir (14.2%) and IVIG (11.36%). Most children did not receive any respiratory support (73.5%) while 9% were placed on invasive ventilation. There were 2,005 patients with final dispositions. Among these, 172 deaths were reported with an 8.6% case fatality rate.

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Most common comorbidities in those who died were neurologic (15.7%), cardiac (12.8%) and hematologic (11.6%) diseases (Figure 1).

Table 4. Treatment and outcomes according to disease severity

| Parameter | | Total (n=2065) | Non-severe (n=1732) | Severe/Critical (n=317) | MIS-C (n=16) |
|---|---|---|---|---|---|
| | | Frequency (%) | | | |
| **Treatment** | Hydroxychloroquine | 8 (0.39) | 5 (0.29) | 3 (0.95) | 0 |
| | Lopinavir-Ritonavir | 6 (0.29) | 4 (0.23) | 2 (0.63) | 0 |
| | Remdesivir | 65 (3.15) | 19 (1.1) | 45 (14.2) | 1 (6.25) |
| | Interferon | 5 (0.24) | 4 (0.23) | 1 (0.32) | 0 |
| | Oseltamivir | 10 (0.48) | 8 (0.46) | 2 (0.63) | 0 |
| | Tocilizumab | 5 (0.24) | 2 (0.12) | 3 (0.95) | 0 |
| | Enoxaparin | 2 (0.1) | 0 | 2 (0.63) | 0 |
| | Antibiotics | 1,198 (58.01) | 883 (50.98) | 299 (94.32) | 16 (100) |
| | Azithromycin | 402 (19.47) | 302 (17.44) | 96 (30.28) | 4 (25) |
| | IVIG | 68 (3.29) | 17 (0.98) | 36 (11.36) | 15 (93.75) |
| | Convalescent plasma | 6 (0.29) | 2 (0.12) | 4 (1.26) | 0 |
| | Corticosteroids | 228 (11.04) | 95 (5.48) | 121 (38.17) | [N=12] |
| | Dexamethasone | 182 (79.82) | 80 (84.21) | 98 (80.99) | 4 (25) |
| | Methylprednisolone | 27 (11.84) | 4 (4.21) | 15 (12.4) | 8 (50) |
| | Hydrocortisone | 21 (9.21) | 10 (10.53) | 11 (9.09) | 0 |
| | Zinc | 1181 (57.19) | 1016 (58.66) | 156 (49.21) | 9 (56.25) |
| | Vitamin D | 825 (39.95) | 695 (40.13) | 122 (38.49) | 8 (50) |
| **Oxygen support** | None | 1518 (73.51) | 1484 (85.68) | 28 (8.83) | 6 (37.5) |
| | Non-invasive | 354 (17.14) | 221 (12.76) | 128 (40.38) | 5 (31.25) |
| | Invasive MV | 193 (9.35) | 27 (1.56) | 161 (50.79) | 5 (31.25) |
| **Outcome** | | [N=2005] | [N=1678] | [N=311] | [N=16] |
| | Discharged | 1650 (82.29) | 1493 (88.97) | 145 (46.62) | 12 (75) |
| | Death | 172 (8.58) | 21 (1.25) | 148 (47.59) | 3 (18.75) |
| | Transfer/HAMA | 183 (9.13) | 164 (9.77) | 18 (5.79) | 1 (6.25) |

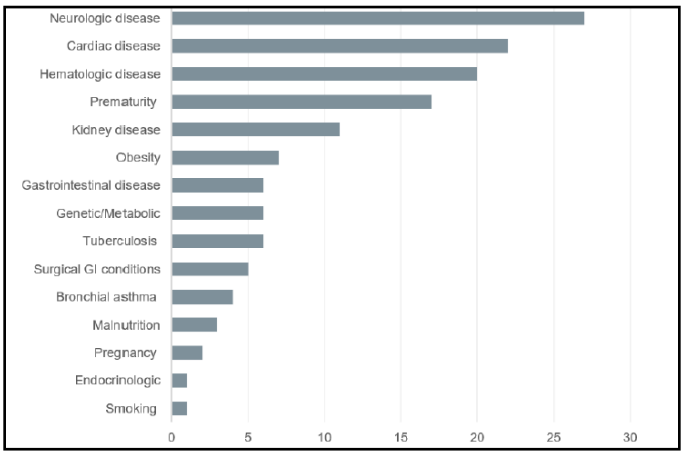

Figure 1. Comorbidities of pediatric COVID-19 non-survivors

## DISCUSSION

We describe the first large-scale cohort study of Filipino children with COVID-19 consisting of 2,127 patients reported to the SALVACION registry, a web-based disease surveillance system for COVID-19 in children in the Philippines.

In this study, majority of cases were between 1 to 5 years old with a median age of 5 years, similar to those reported by Nachega, *et al.* in a cohort of sub-Saharan African children and in those reported by Lu, *et al.* among children in Wuhan.[11-12]

This was lower than the median age of 11.9 years reported by Martin, *et al.* in the US.[13] A slight male predominance at 57% was observed in our study, similar to previous reports.[11,12]

Mild and moderate diseases were noted in majority of cases, while severe and critical diseases comprised 15.2% of cases, comparable to the report of Martin, *et al.* where 13.9% met the criteria for severe disease.[13] This was lower than the 47.5% reported by Nachega.[11] The rate of asymptomatic infection was 17.1%, lower than that reported by Chen, *et al.* (32.1%) and Lu, *et al.* (26.4%), which may be attributed to underreporting of asymptomatic cases or lack of testing of asymptomatic children due to inaccessibility, cost or prioritization of symptomatic household members for testing.[12,14] MIS-C cases represent 0.7% of reports, consistent with the study of Dufort, *et al.* (0.6%).[15] MIS-C was most commonly reported in children 6 to 10 years old with a median age of 8 years, consistent with reports of Hoste, *et al.*, Radia, *et al.* and Sharma, *et al.*[16-18]

Tsankov, *et al.* reported that children with comorbidities are 1.79 times more likely to develop severe COVID-19 and/or be admitted to the PICU and 2.8 times more likely to die.[19] In our study, the most common comorbidities in children with severe and critical COVID-19 and among those who died were neurologic disease, hematologic-oncologic disease and cardiac disease. Neurologic disease was also reported by Martin, *et al.*, but concluded that neurologic comorbidities were not significant predictors of severe disease, contrary to our findings.[13] A systematic review by Schlage, *et al.* on COVID-19 and pediatric cancer reported that COVID-19 infection in pediatric cancer patients resulted in severe disease in only a minority of patients; however, despite a milder course, mortality rate was higher than in children with no comorbidities, with deaths attributable to either COVID-19 complications or cancer progression.[20]

In another study by Williams, *et al.*, cardiac comorbidities were most common in children with severe and critical COVID-19.[21]

Among MIS-C cases, obesity was the most common comorbidity, consistent with the report of Hoste, *et al.*[16] With obesity being associated with a chronic subclinical inflammatory status, it is hypothesized that COVID-19 infection triggers a greater hyperinflammatory response and higher endothelial, macrophage and adipocyte activation, leading to considerably elevated inflammatory markers and more severe complications.[22,23]

Fever, cough, and colds were the predominant symptoms. However, gastrointestinal symptoms were also commonly reported, similar to those of Lu, *et al.*[12] Inflammatory markers (CRP, procalcitonin and D-dimer) and markers for organ dysfunction (AST, ALT and LDH) were significantly higher in severe and critical disease compared to non-severe disease, similar to the study of Martin, *et al.*[13] Radiographic findings were mostly normal, as reported in other studies.[24] However, Serrano, *et al.* noted bilateral diffuse peribronchial cuffing as the most common finding, followed by diffuse ground glass opacities.[25]

In the study by Mohammadi, *et al.*, two-thirds of patients have abnormal chest CT scan results, with consolidation and ground-glass opacities.[26] This was lower in our study at only 48.7%, but ground-glass opacities were also the most common finding.

Systemic corticosteroids were the most commonly used immunomodulatory agent in our study with 11% of patients receiving this medication. Among those given systemic corticosteroids, 53.1% had severe/critical COVID-19. About 75% of MIS-C patients were also treated with systemic corticosteroids. This is consistent with the Philippine COVID-19 living recommendations and the PIDSP guidelines, which support the use of systemic corticosteroids (dexamethasone) among children with severe and critical COVID-19.[27,28]

Remdesivir was the most commonly used antiviral agent, given to 14.2% of severe/critical COVID-19 patients, while intravenous immunoglobulin was given to 93.75% of patients diagnosed with MIS-C, following local recommendations.[28]

Our findings showed a high prevalence of antibiotic use, with 58% of patients receiving at least one type of antibiotic. Antibiotic use in children with COVID-19 has been reported to range from 24.5% in a cohort in Latin America to 64% in a cohort in the UK.[29,30] Increased use of antibiotics was seen in children with fever, in those who were hospitalized, had ARDS or abnormal chest x-ray findings, required intensive care, oxygen support (non-invasive or invasive ventilation) and diagnosed with MIS-C with or without cardiac involvement.[29] In our study, antibiotic use was higher in those with severe and critical COVID-19 and MIS-C, likely because symptoms and laboratory findings of these conditions overlap with sepsis; hence, differentiation may be difficult without the benefit of culture results. The increased use of antibiotics during the pandemic has raised the alarm globally on its effect on antimicrobial resistance rates, and antimicrobial stewardship strategies must be incorporated into the management of all children with COVID-19.[31]

The case fatality rate (CFR) in our cohort was 8.6%, higher than that reported by the Philippine's Department of Health among pediatric cases (0.3%), as well as by Kitano, *et al.* in a study of pediatric COVID-19 fatalities in high-income (HIC) and low- and middle-income countries (LMIC).[32] The global estimated pediatric CFR was 0.061%, with LMICs having a significantly higher CFR (0.29%) than HIC (0.03%). Our CFR may be overestimated, as most of the cases reported were hospitalized patients (89%) with comorbidities, predisposing them to severe and critical disease and a higher risk for mortality.

This study has several limitations. The SALVACION registry is used for passive surveillance of cases reported voluntarily by physicians handling pediatric COVID-19. Cases are grossly underreported, as our database only represents 0.6% of the total number of pediatric COVID-19 cases based on the Department of Health's COVID-19 tracker. In addition, almost 50% of reports came from tertiary hospitals and COVID-19 referral centers in the National Capital Region; hence, data may not reflect the overall epidemiology of pediatric COVID-19 in the country. Second, since most reported cases are hospitalized children and children with comorbidities, findings such as disease severity, presence of underlying conditions, use of immunomodulatory treatment options and case-fatality rates may be overestimated and must be interpreted with caution. Third, since data is submitted voluntarily and aggregated from different health facilities, some data may be unavailable or unreported. There may also be limited access to laboratory tests and diagnostic procedures in some regions and laboratory results may not be standardized due to different laboratory analytical techniques and processes.

The SALVACION registry continues to accept reports and data collection is still ongoing. At present, the registry has provided data to national health authorities and specialty medical societies to guide policy decisions on pediatric vaccination and create clinical guidelines and resources on the care for children with COVID-19. Data from the registry also stimulate research and help identify gaps in knowledge for further investigation.

## CONCLUSION

Pediatric COVID-19 cases reported to the SALVACION registry are generally mild to moderate in severity. Among severe and critical cases, the most common comorbidities are neurologic, hematologic-oncologic and cardiac diseases. Most patients recovered with supportive management.

High antibiotic usage was seen, which warrants emphasis on judicious antimicrobial use in this cohort.

## ACKNOWLEDGEMENTS

This study was funded by the Pediatric Infectious Disease Society of the Philippines and is dedicated to our past president, Dr. Salvacion R. Gatchalian, after whom the registry was named. The registry serves to honor her legacy after she passed on due to COVID-19 in March 2020, while serving as the president of the Philippine Pediatric Society. The authors also wish to acknowledge the following for their substantial contributions to the fruition of the registry: Beverly Alejandro-Pelino, Noreen Cala-Mayubay, Justin Ho, Jasmin Nadorra-Dela Cruz and Princess Elham Sacar for data encoding; 2) Razel Custodio and Juvar Abrera for website development; and 3) Juztin Del Rosario for statistical analysis.

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https://doi.org/10.56964/pidspj20222302007

**ORIGINAL ARTICLE**

# THE ETIOLOGY OF CHILDHOOD INPATIENT PNEUMONIAS IN TWO PRIVATE, TERTIARY, METRO MANILA HOSPITALS FROM 1993-2021 SEEN BY ONE PEDIATRIC INFECTIOUS DISEASE SPECIALIST

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## ABSTRACT

**Introduction:** The scarce local data on the etiology of childhood pneumonia admitted in a hospital has come from a few urban and rural government hospitals. There is no data from private hospitals. Knowing the most likely etiology of pneumonia is of outmost importance as this has implications on the diagnostic modalities requested and the institution of therapy.

**Objectives:** The purpose of this study is to identify clinical and microbiologic diagnoses of clinically- and radiographically-confirmed pediatric pneumonia cases admitted in a private hospital. Secondarily, a discussion of specific etiologies is made.

**Methodology:** Each consecutive, inpatient, pneumonia referral/admission in either one of two private, urban, tertiary hospitals, of a child 18 years and below from 1993 to 2021 was logged into a computer daily by a single pediatric infectious disease specialist. Clinical, epidemiologic, diagnostic and therapeutic data were recorded. All pneumonia cases, except those seen in newborns before their discharge from the nursery, were included.

**Results:** Of the 496 cases**,** there was a clinical and/or microbiologic etiology in 43% of cases. The bacteremia rate was 6.3%. The most common identifiable etiologies were *Mycoplasma pneumoniae* (11.9%), *Mycobacterium tuberculosis* (5.2%), and *Staphylococcus aureus* (4.2%), while bronchiolitis (5.5%) and measles (4.8%) were the most common clinical diagnoses. There were several cases of ventilator-associated pneumonia and *Pneumocystis jirovecii* pneumonia.

**Conclusions:** *Mycoplasma pneumoniae*, tuberculosis, *Staphylococcus aureus* and *Pneumocystis jirovecii* are important pneumonia etiologies that have not been widely considered locally. The data presented here mirrors the practice of one pediatric infectious disease doctor in two hospitals where diagnostic and treatment options are readily available and utilized.

**KEYWORDS:** *Etiology; Pediatric Community Acquired Pneumonia*

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The author declares that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by the author, and that the author has met the requirements for authorship.

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## INTRODUCTION

Childhood pneumonia is generally treated empirically, often based on data from the West, or from WHO data that was based on third world reports which were mostly from the 1980s and 1990s.[1] The scarce local data on etiology of pneumonia have been reported from Metro Manila government hospitals (Philippine General Hospital [PGH], Philippine Children's Medical Center [PCMC], Regional Institute for Tropical Medicine [RITM], and Quezon City General Hospital [QCGH]) and rural government hospitals from Bohol and Tacloban.[2-5] There is no data from private hospitals.

The 2021 PAPP-PIDSP Clinical Practice Guidelines in the evaluation and management of Pediatric Community-acquired Pneumonia (PCAP) indicated that there is a lack of local data on PCAP etiology, and do not include viruses other than influenza, bacteria like pertussis and *Mycoplasma pneumoniae*, specifically; and fungi like *Pneumocystis jirovecii*; and only briefly mentions *Staphylococcus aureus* and *Mycobacterium tuberculosis* as possible pneumonia etiologies. The PCAP guidelines are a classification of community-acquired pneumonia in children, based on clinical assessment of disease severity, and its corresponding treatment; etiology is not emphasized as much due to the dearth of published information.[6] In an era where there is a heightened awareness of the need for rational antimicrobial use due to high rates of multi-drug resistant organisms seen in hospitals and the community, an improved knowledge of the likely organism(s) involved in a specific type of pneumonia, will allow the clinician to choose antimicrobials, if necessary, that are more specifically directed to such an organism or organisms.

The primary objective of this study is to provide local data on specific etiologic organisms and clinical diagnoses of all pneumonia cases admitted and seen by a single pediatric infectious disease practitioner over a 29-year period.

Secondarily, a discussion of specific etiologies is made.

## MATERIALS AND METHODS

Cases in this paper included all cases of pneumonia compiled from 1993 to 2021. Each consecutive inpatient admission or referral of a patient 18 years or younger was routinely logged into a personal computer daily. Cases in which a discharge diagnosis of pneumonia of any severity together with the eventual identified etiology to explain the pneumonia (if any was arrived at) were included in this study. Clinical, epidemiologic, diagnostic and therapeutic data relevant to the pneumonia diagnosis were routinely recorded in each patient's account. The inclusion criteria for pneumonia were a child with cough, with or without tachypnea, with or without fever, and with a chest radiograph showing evidence of acute lung parenchymal disease. The etiologic diagnosis was made as follows:

- Bacterial organisms (from blood, sputum, pleural fluid, endotracheal aspirate) by standard laboratory methods
- Mycoplasma disease by the Immunocard Mycoplasma IgM$^{R}$ test
- *Pneumocystis jirovecii* by a methenamine silver stain of Gomori, direct fluorescent antigen stain or by PCR testing
- Tuberculous (TB) pneumonia based on clinical findings, a positive 5 TU PPD test or serum TB Quantiferon result, characteristic radiographic findings, epidemiology, and laboratory findings (positive AFB smear, TB GeneXpert$^{R}$, and/or identification of *Mycobacterium tuberculosis* in culture)
- Leptospirosis by the presence of serum IgM antibody
- COVID-19 infection by a COVID RT-PCR test from a nasopharyngeal and oropharyngeal swab
- Influenza virus by a rapid point-of-care antigen test
- Pertussis, bronchiolitis, measles and varicella were identified clinically

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Although as a general statement, diagnostic tests were largely done as needed, without concern for cost, the diagnostic tests varied according to clinical state and epidemiology. In general, a blood culture was done for all patients referred to the author.

Excluded were newborns born at the study institutions with pneumonia, who had not been discharged from the nursery yet. Cases with a diagnosis of primary TB, without a clinical and progressing pneumonia, were excluded.

This study was approved by each hospital's Institutional Review Board. As all the cases were obtained from the author's personal files in a password-protected personal computer, no medical records were accessed from the hospitals' medical records department.

The author has no conflict of interest in the conduct of this study.

## RESULTS

Table 1. Etiology of childhood inpatient pneumonia cases seen by one pediatric infectious disease physician from 1993 to 2021, from two private, urban, tertiary hospitals. *(N=496)*

| Etiology (source) | No. (%) |
|---|---|
| *Mycoplasma pneumoniae* | 59 (11.9%) |
| Bronchiolitis (clinical) | 27 (5.5%) |
| *Mycobacterium tuberculosis* | 26 (5.2%) |
| Measles (clinical) | 24 (4.8%) |
| *Staphylococcus aureus* | 21 (4.2%) |
| Blood culture-positive | 14 |
| Pleural fluid culture-positive | 7 |
| *Bordetella pertussis* (clinical) | 12 (2.4%) |
| Influenza AH1N1 antigen positive | 8 (1.6%) |
| *Pneumocystis jirovecii* | 7 (1.4%) |
| *Streptococcus pneumoniae* (blood) | 6 (1.2%) |
| *Salmonella spp.* (blood) | 6 (1.2%) |
| COVID-19 (RT-PCR positive) | 6 (1.2%) |
| Varicella (clinical) | 4 (0.8%) |
| Leptospirosis (serum leptospirosis IgM) | 2 (0.4%) |
| *Serratia marcescens* (blood) | 2 (0.4%) |
| *Mycobacterium abscessus* (B.A.L. aspirate and mycobacerial culture) | 1 (0.2%) |
| *Pseudomonas spp.* (blood) | 1 (0.2%) |
| *Stenotrophomonas maltophilia* (blood) | 1 (0.2%) |
| *Chromobacterium anthropi* (blood) | 1 (0.2%) |
| *Rhizopus spp.* (lung biopsy and fungal culture) | 1 (0.2%) |
| No etiology | 281(56.7%) |

Table 2. Endotracheal aspirate growths in children with ventilator-associated pneumonia seen by one infectious disease physician from 1993 to 2021, from two private, urban, tertiary hospitals. *(N=26)*

| Organism | No. (%) |
|---|---|
| *Pseudomonas aeroginosa* | 7 (27%) |
| *Klebsiella spp.* | 3 (12%) |
| *Staphylococcus aureus* | 3 (12%) |
| *Serratia marcescens* | 3 (12%) |
| *Stenotrophomonas maltophilia* | 2 (8%) |
| *Candida spp.* | 1 (4%) |
| *Acinetobacter spp.* | 1 (4%) |
| *Enterobacter aerogenes* | 1 (4%) |
| No growth | 5 (19%) |

## DISCUSSION

Ninety-eight percent of the cases in this study were referrals to the author from general pediatricians and the rest are the author's own patients. This 29-year retrospective study of childhood inpatient pneumonia in two private, urban, tertiary hospitals found a clinical and/or microbiologic etiology in 43% of the 496 cases. Of those with a known cause, the most common etiologies were *Mycoplasma pneumoniae* (11.9%), bronchiolitis (5.5%), *Mycobacterium tuberculosis* (5.2%), measles (4.9%) and *Staphylococcus aureus* (4.8%). Endotracheal growths for mechanically-ventilated children, tabulated separately, showed mostly gram-negative bacillary growths and *S. aureus*. The bacteremia rate was 6.3%.

### I. Viral Pneumonia

Community-acquired pneumonia is defined as an illness with signs and symptoms of an acute infection of the pulmonary parenchyma, while bronchiolitis is broadly defined as a clinical syndrome of respiratory distress that occurs in children <2 years of age and is characterized by upper respiratory symptoms eventually followed by lower respiratory (e.g., small airway/bronchiole) infection with inflammation. Bronchiolitis is generally caused by several viruses, the most common of which is RSV. RSV bronchiolitis is often indistinguishable from RSV pneumonia and, frequently, the two coexist.[7]

With this significant overlap in the clinical manifestations, the author included bronchiolitis under the viral pneumonias in this paper.

Bronchiolitis was the second most frequent diagnosis (5.5%). This is a common viral lower respiratory tract illness usually seen in children less than two years of age, with its highest incidence between 6 weeks to 7 months. The hospitalization rate for healthy infants with RSV bronchiolitis is 0.5-4%.[7] In the present study, although our laboratory can identify RSV by PCR testing at the present time, all the bronchiolitis cases were seen before PCR testing was available, so that none of the cases was documented to be due to RSV. In studies from Tacloban City and Baguio City among children with severe inpatient pneumonia in whom viruses were identified, RSV was the virus present in 24% and 88% of cases, respectively, when a virus was isolated. Disease peaked in October, and 70% of RSV cases were seen in children aged <1 year, while 23% were between 1-2 years.[5,8] In a study in Metro Manila of infants <90 days of age evaluated for sepsis, pneumonia, or meningitis, for whom viruses were identified, RSV-positive cases were seen from July to October, with a peak in October.[4] The illness usually manifests with rhinorrhea, cough and an inconsistent fever, progressing over 2-5 days to tachypnea, wheezing, chest retractions and cyanosis; chest radiograph will usually show hyperinflation, bilateral interstitial infiltrates, and peribronchial cuffing.[7] In Tacloban City, the case-fatality rate for RSV-positive children was 7.5%.[5] Other known causes of bronchiolitis are human metapneumovirus, rhinovirus, parainfluenza, influenza, bocavirus and adenovirus.[7]

Measles-associated pneumonia was the 4$^{th}$ most frequent etiology, seen in 4.8% of cases. Locally, during a measles outbreak, pneumonia cases can rise sharply. It is generally difficult to distinguish a purely measles pneumonia from a measles pneumonia complicated by a secondary bacterial pathogen.

All of the measles pneumonia cases reported in this study were empirically treated with antibacterial due to the recognized significant morbidity and mortality accompanying such cases. In an RITM study of 537 children <5 years of age admitted for pneumonia, 48% had measles; among the measles cases, 14.8% had bacteremia, with *Salmonella spp*. and *Haemophilus influenzae* most commonly identified.[2] In a National Children's Hospital study, among the 425 pediatric inpatients admitted for measles, 77% developed pneumonia. Of these, 15% were 0-6 months of age, 34% were 7-12 months of age, and 28% were 13-23 months of age. Younger age (18 months for measles pneumonia vs. 37 months for measles alone), wasting and stunting were associated with an increased risk for measles pneumonia.[9] In a study from RITM of 71 children under five years of age who died of pneumonia, 35 children (49%) had clinically diagnosed measles. To determine the etiology of death for those with measles, ante-mortem blood culture, lung aspirate culture, post-mortem lung swab culture, and tissue gram stain were done; 25% of the children had measles virus only isolated, 43% had measles virus with bacterial super-infection, and 29% had bacteria only isolated.[10] Of the bacterial infections complicating measles, *S. aureus* was identified in 12 of 35 (34%) and *Pseudomonas aeruginosa* in 8 of 35 (23%); all of the *P. aeruginosa*-measles cases had received antibacterial at home before being admitted.[10]

Influenza with pneumonia was seen in 1.6%; most of the cases were seen during the 2009 influenza AH1N1 pandemic when the cases were documented to have the virus as reported in a previous study from one of the institutions in the present study.[11] In local reports, among severe pneumonia cases in whom viruses were specifically identified, a study in Baguio City of 377 children under six years isolated Influenza B in 6%, Influenza A in 4%, and Influenza AH1N1 in 2%.[8]

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In a study done in Tacloban City of 819 children under 14 years with pneumonia, Influenza A was identified in 2.2%.[5] During the 2009 Influenza AH1N1 pandemic, three local studies showed that 2%, 2.5% and 14% of children documented to have Influenza AH1N1 infection developed clinical and/or radiographic pneumonia.[8,12-13] In Baguio City and Metro Manila studies among children with influenza pneumonia, ages were <5 years old in 9-20%; 6-10 years old in 23-33%; 11-15 years old in 32%;[11-12] this is unlike RSV bronchiolitis, in which children are <2 years of age. Locally, children with documented influenza infection have fever (92-100%), cough (80-85%), colds (47-76%), throat pain (33-42%), vomiting (8-22%), headache (18-19%), diarrhea (4-18%), dyspnea (7%) and respiratory failure (0-1.5%).[11-13]

Pneumonia was due to COVID-19 in 1.2% of children in this study. All had a known adult exposure at home, had minimal radiographic infiltrates, and all recovered from the pneumonia. Four of the six children were between 8-22 months of age. The other two were both 13 years old; one was initially admitted for hemophagocytic lymphohistiocytosis, whose illness was complicated by COVID-19 infection, Multisystem Inflammatory Syndrome in Children (MIS-C), and a mild pneumonia; the second adolescent was undergoing chemotherapy for acute myelogenous leukemia and developed COVID-19 infection and a mild pneumonia. Both recovered from COVID-19. Children are far less infected by COVID-19 infection compared to adults, and when the former are infected, they often have a mild illness which does not require hospitalization; rarely is intensive care treatment necessary.[14-16]

Varicella pneumonia was seen in 0.8%. Varicella is known to be complicated by skin and soft tissue infections, pneumonia and encephalitis. Pneumonia has been reported in 6%, 8% and 17% of children admitted for varicella complications, and one population-based estimate of varicella pneumonia indicated a rate of 4.3 cases per 10,000 varicella infections.[17-19]

Due to the market population of the two hospitals, there is a high likelihood that a big proportion of the children catered to were vaccinated for varicella, to explain the low rate of cases admitted with varicella pneumonia. Like the measles virus, varicella virus causing pneumonia versus a secondary bacterial infection complicating the disease is hard to distinguish. These cases were admitted and given antimicrobials, and treated as varicella with secondary bacterial pneumonia.

**II. Community-Acquired Bacterial Pneumonia**

Bacteremia and/or a pleural fluid growth occurred in 7.7% of cases, with *S. aureus* (4.2%), *S. pneumoniae* (1.2%) and *Salmonella spp.* (1.2%) being the only blood culture isolates in community-acquired pneumonia in this study. Worldwide, the microbiologic etiology of childhood pneumonia has always been an enigma because the gold standard, obtaining lung samples through an invasive procedure like a percutaneous lung aspirate for specimen collection, is accompanied by significant risks and costs. On the other hand, more readily available tests, sputum culture and blood culture, are often not available or have a low yield: most children under six years cannot be expected to provide a good sputum sample. Blood cultures are known to grow a pathogen only infrequently, with bacteremia only detected in 2.3% to 3.9% in the West.[20-21] At the RITM, among children <5 years of age admitted with pneumonia, 44% had an identified etiology and the bacteremia rate was 13%.[2] In a multi-center study from PGH, QCGH and RITM of infants <3 months old with severe pneumonia, the bacteremia rate was 7%;[4] in a study done in Bohol of infants <2 months of age, the bacteremia rate was 5%;[3] while in a study done in Tacloban City of children <14 years old, it was 2.9%.[5]

*Staphylococcus aureus* was the 5th most common pneumonia etiology (4.8%) identified and was the top cause of community-acquired bacteremic pneumonia.

Children often had pyoderma as a primary focus (skin abscesses, intravascular catheter-related phlebitis, cellulitis, or fasciitis), while the pleural isolates were from pleural extension of staphylococcal pneumonia, usually with pneumatocoeles on radiography, or through downward extension of complicated neck infections (neck abscess, Ludwig's angina, and subsequent mediastinitis) as was seen in a previous report from one of the institutions in this study.[22] Locally, a rural PCAP study in Tacloban City of children <14 years old, who were admitted, reported a *S. aureus* growth in 0.5% of blood cultures.[5] In a study done at PCMC, among all *S. aureus* isolates from different body fluids, 17% were obtained from pneumonia and empyema cases; 7% were isolated from blood.[23] In a study done at RITM of 71 fatal pneumonias seen in children under 5 years of age, *S. aureus* was the most commonly identified organism, with 13 obtained from ante-mortem blood culture and 7 from tissue; 61% of the staphylococcal pneumonia cases were associated with measles, while the rest were associated with a primary skin lesion.[10] In a World Health Organization (WHO) programme report on ARI, a study of blood isolates from 167 of 8,418 infants with pneumonia from Gambia, Papua New Guinea and Philippines was cited, and the top organisms reported were *S. aureus* (20%), Group A Streptococcus (17%), *E. coli* (11%), *Salmonella spp*. (10%) and *H. influenzae* (4%).[24] Known risk factors for *S. aureus* pneumonia are untreated skin and soft tissue infections, *S. aureus* bacteremia, measles, influenza and pertussis.[25] Radiographically, *S. aureus* pneumonia may distinctively show cavitations, pneumatocoeles and pleural effusion or empyema.

Clinically diagnosed pertussis with pneumonia was seen in 2.4%. These patients were mostly infants under six months of age who had not finished their primary pertussis vaccination series.

In a study done at the PGH, 93% of pertussis admissions were less than four months old, and 36% were not even old enough to have received their first DPT vaccine.[26] Infants <2 months old who get pertussis have the highest hospitalization rates, with 25% developing pneumonia, and mortality is 1%.[27] Other than age, clues for pertussis are the absence of fever despite a radiographic pneumonia, the paroxysmal nature of the attacks of coughing, a peripheral leukocytosis with a lymphocytic predominance, thrombocytosis, a radiograph which may only be mildly abnormal with a perihilar infiltrate and/or atelectasis, and the presence of a recent or ongoing cough among the infant's caretakers. Consolidation in the radiograph of an infant with pertussis suggests a secondary bacterial infection due *S. aureus*, *S. pneumoniae* and/or oropharyngeal flora.[27]

*Streptococcus pneumoniae* was the 9th most frequent etiology, identified by blood culture in 1.2%. This organism has traditionally been the top cause of bacterial PCAP, although this has not been reflected in local studies. In a study done in Bohol, the bacteremia rate for infants <2 months of age admitted with pneumonia was 5%, with only 1.3% being due to *S. pneumoniae*.[3] In a Metro Manila study of children <5 years of age with suspected invasive bacterial disease, 0.8% grew *S. pneumoniae* in blood culture.[28] In a PGH-RITM-QCGH study of infants <3 months of age admitted for sepsis, pneumonia or meningitis, among 198 who had pneumonia, 7% were bacteremic but only one blood culture grew *S. pneumoniae* (0.5%).[4] In a study done in Tacloban City of children <14 years old with severe pneumonia, only 0.5% had a blood culture growth of *S. pneumoniae*.[5] In a study done in Central Visayas of 956 children <6 years old with pneumonia, sepsis and/or meningitis, 1.3% grew *S. pneumoniae*, with 9 of 12 invasive pneumococcal isolates seen at age 12 months or younger.[29] These numbers are less, but not far from, those reported in the West.

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In Spain, 2.1% of 884 children admitted with community-acquired pneumonia grew *S. pneumoniae* in blood cultures, while in the U.S., the rate was 2.8% among pediatric community-acquired pneumonia cases admitted to four large Children's Hospitals.[20-21] In this study, only 23% of all growths in blood cultures for community-acquired pneumonia was due to *S. pneumoniae*. Among all blood culture growths in other local reports, *S. pneumoniae* was the growth in 14% in Tacloban City and 27% in Bohol.[4-5] Even as this organism is considered to be the most common pathogen for pneumonia at 3 weeks to 4 years of age,[30] much of this data was obtained in the 1980s and 1990s using poorly validated body fluid antigen and antibody tests.[21]

*Salmonella spp*. bacteremia with pneumonia was seen in 1.2%; all were in infants <12 months of age. Non-typhoidal salmonella is known to be potentially invasive when infection occurs in infancy. Among 198 infants <90 days of age with inpatient pneumonia at PGH, QCGH and RITM, 7% had a positive blood culture growth; of these, *Salmonella spp.* was the top growth (3 of 14; 21%). Half of the infants who had salmonella bacteremic pneumonia were born at home.[4] Among children <14 years old in Tacloban City with severe pneumonia, only 2.3% were bacteremic; of the 17 with bacteremia, one was due to Salmonella spp.[5] In other countries, among 1,032 children <6 years old in Ghana admitted for pneumonia, 9% of 173 children who were bacteremic grew a non-typhoidal salmonella, even more frequent than bacteremic *Streptococcus pneumoniae* (4.6%).[31] Among 152 Thai children <16 years old with inpatient PCAP, only six (3.9%) were bacteremic, with blood culture growths of *S. pneumoniae*, *E. coli* and *Salmonella* group B.[32] As salmonella is not generally a respiratory pathogen, the pneumonia seen in salmonella-bacteremic infants is possibly a complication of the bacteremia.

Leptospirosis with pneumonia was seen in 0.4%; neither of the two cases was suspected to have pulmonary hemorrhage. Leptospirosis can be accompanied by pneumonia in 6-50% of cases, and pulmonary symptoms include cough, shortness of breath, cyanosis and hemoptysis.[33-35] Among the 85 children with leptospirosis in Tondo General Hospital, 14% had cough or dyspnea, but there was no mention of pneumonia.[36] A known complication of leptospirosisis is pulmonary hemorrhage, which may bring about radiographic infiltrates and acute respiratory distress syndrome.[33-35]

*Haemophilus influenzae* type B (HiB) is a known pneumonia pathogen, but was not identified in this series. The organism is known to cause a low-grade intermittent bacteremia and is rarely cultured from blood. The clientele in the two hospitals are known to be in the middle-class socio-economic bracket, with a high likelihood to have received HiB vaccination, to possibly explain the absence of documented HiB cases. Locally, a rural study among children <6 years of age with pneumonia reported HiB in 1.3% of blood cultures, with 11 of 12 cases seen in children <1 year of age.[29]

Among the above community-acquired bacterial pneumonia etiologies, all can be seen in the first 12 months of age. As children get vaccinated for HiB and pertussis, these two are less likely to be seen after five to six months of age. Salmonella can be seen sporadically and may be influenced by socio-economic factors and young age; pneumonia is likely secondary to bacteremia. *Staphylococcus aureus* pneumonia is associated with untreated pyodermas and *S. aureus* bacteremia. Radiography will not generally distinguish bacterial etiology, but when pneumatocoeles are present, the etiology will likely be *S. aureus*.

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https://doi.org/10.56964/pidspj20222302007

After age 12 months, in DPT-HiB-vaccinated communities, *S. pneumoniae* becomes the predominant community-acquired bacterial pathogen, as current pneumococcal vaccines do not prevent disease due to non-vaccine pneumococcal serotypes and pneumococcal vaccines are not routinely available in most local health centers.

**III. Atypical Pneumonia**

*Mycoplasma pneumoniae* was the top pneumonia etiology (11.9%) identified. In four local pneumonia studies on admitted patients, three of which were done in the same two institutions in this study, this organism was detected in 4%, 22%, 26% and 28% of childhood inpatient pneumonias.[37-40] In one published prospective local study of PCAP in children under six years of age, *Mycoplasma pneumoniae* was detected in 26%, indicating that this organism is not only seen in older school-aged children.[38] In the West, *Mycoplasma pneumoniae* has been reported to cause 20% of PCAP among high school students and is considered to be the most commonly identified bacterial pathogen for children 5 years of age and older.[41] The local studies, including the present one, used a serologic IgM test, which is known to show a positive result for up to 6-12 months after the acute infection. Pneumonia due to *Mycoplasma pneumoniae* is generally indistinguishable from other bacterial pneumonia causes, but a clue may be a normal WBC count in the presence of a moderately elevated ESR and/or CRP.[39-41] Chest radiograph often shows an interstitial pneumonia, but it may also appear as bronchopneumonia.[39-41] The organism, in general, does not cause a hypoxemic illness, thereby causing a classical “walking” pneumonia.

Though the study hospitals can now identify chlamydophyla by PCR testing, no cases had been identified at the time of this study, as no other chlamydophyla testing kits were available over the previous 25 years.

**IV. Ventilator-Associated Pneumonia**

Blood culture grew gram-negative bacillary organisms (*Serratia marcescens*, *Pseudomonas spp.*, *Stenotrophomonas maltophilia* and *Chromobacterium anthropi*) among children with pneumonia in this study (1% of cases); all were treated for healthcare-associated pneumonia. For ETA isolates (see Table 2) from mechanically-ventilated children, *Pseudomonas aeruginosa* was the top isolate with 26%, followed by *Klebsiella spp.*, *S. aureus*, *B. cepacia* and *S. marcescens* at 12%, each. In a study done in Cebu of 343 children <6 years old with severe PCAP who were intubated and mechanically ventilated, in which an ETA culture was obtained within three days of admission (which the authors considered to be community-acquired infections), 19% had a growth, with the organisms being *Klebsiella pneumoniae* (38%), *P. aeruginosa* (26%), *Acinetobacter baumanii* (15%), *Enterobacter cloacae* (12%) and *S. aureus* (6%). Of those with an ETA growth, 92% had been given antibiotics at home.[42] Hospital-acquired gram-negative bacilli are the usual causes of ventilator associated pneumonia. Risk factors are neurologic incompetence, seizure disorder, surgery, inappropriate feeding of children in respiratory distress, prior antibiotic use and contaminated respiratory equipment.[43] The usual clinical manifestations are a new-onset fever in a hospitalized child who has new radiographic infiltrates, an increasing oxygen requirement, and leukocytosis.[43] The patients in this study were mostly neurologically impaired due to infection or seizures, or were post-operative cases which entailed extended mechanical ventilation support. The organisms obtained in ETA culture are similar to other reports in the literature, in which gram negative bacilli, notably *P. aeruginosa* and *Klebsiella spp.,* and *S. aureus* are the predominant isolates.[44-45]

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 43-54 July-December 2022
Garcia RDJ. The Etiology of Childhood Inpatient Pneumonias in Two Private, Tertiary, Metro Manila Hospitals from 1993-2021 Seen By One Pediatric Infectious Disease Specialist
https://doi.org/10.56964/pidspj20222302007

In a local study done where post-mortem lung aspiration was performed in 50 children who died of very severe pneumonia, the top four isolates were *Pseudomonas spp.* (28%), *Enterobacter spp.* (18%), *S. aureus* (11%), *E. coli* (10%) and *Klebsiella spp*. (8%). However, the authors did not indicate if these were ventilator-associated or community-acquired; 52% of the patients were in the hospital for more than seven days before death and 86% were infants.[46]

**V. Tuberculous Pneumonia**

Tuberculous pneumonia was the third most common etiology (5.2%) in this study. It is important to be aware that TB can cause pneumonia, especially in the local setting. In this study, cases often manifested as a sub-acutely evolving (2-6 weeks) illness with clinical and radiographic pneumonia, usually with prolonged fever, productive cough, with poor response to different oral and intravenous antimicrobials and, often, with an adult pulmonary TB contact at home, which are findings similar to that reported in the literature.[47] In the present study, continued fever despite one or more courses of oral antibiotics was usually the reason for the hospital admission. Otherwise, a frequent observation among the TB pneumonia cases was that these children were usually not hypoxemic, despite a prolonged illness. The availability of the TB GeneXpert$^{R}$ test has greatly aided in a more prompt diagnosis of TB pneumonia because prior to its availability, it would take 3-5 weeks before a sputum mycobacterial culture yielded the diagnosis if the initial acid-fast bacilli (AFB) smear was negative. Clinically, TB pneumonia may be seen in two situations: progressive primary TB pneumonia occurring in very young infants who have marked weight loss, fever, cough and fatigue; while reactivation TB with pneumonia is usually seen in older children and adolescents who have fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis and chest pain.[48-49]

Radiographically, TB pneumonia is indistinguishable from other causes, unless thick-walled cavities, usually in the upper lobes, are seen, in older children; pleural effusion may be present.[48]

In this study, there was one case of *Mycobacterium abscessus* pneumonia in a diabetic 18-year-old girl with a 12-year history of achalasia and repeated aspiration pneumonia. The organism was obtained through bronchoalveolar lavage. She presented with a 4-month long fever, like what is seen with TB pneumonia, but she did not respond to anti-TB medications nor did she have a documented TB contact at home. When the mycobacterial susceptibility result was obtained, her medications were adjusted and she recovered after the treatment course.

**VI. *Pneumocystis jirovecii* and Other Fungal Pneumonia**

There were seven cases (1.4%) of *Pneumocystis jirovecii* pneumonia, none of whom had HIV infection. One was a 13-month-old girl with post-measles pneumonia complicated by respiratory failure. A 2$^{nd}$ case was a 4-year-old girl with severe pneumonia and respiratory failure; she was found to have CD4-lymphocytpenia but her HIV test was negative. A 3$^{rd}$ case was a 17-year-old male with fever of unknown origin for four weeks and insidious pneumonia, who was found to have CD4-lymphocytopenia but was HIV-negative. A 4$^{th}$ case was a 6-month-old preterm boy with bronchopulmonary dysplasia, who had three pneumonia episodes after being discharged from the nursery at three months of age; during the 3$^{rd}$ pneumonia episode, he was found to have pneumocystis. A 5$^{th}$ case was a 6-year-old boy with Acute lymphocytic leukemia who developed pneumonia after intensive chemotherapy. A 6$^{th}$ case was a 5-year-old with a sellar tumor who was on radiotherapy and corticosteroid treatment. A 7$^{th}$case was a 1-year-old with severe combined immunodeficiency.

All cases had the organism identified from an endotracheal aspirate, except for the 3rd case for whom a sputum sample was the source. Of the seven cases, three died even with the standard care provided. Risk factors for pneumocystis pneumonia are HIV/AIDS and other T-cell immunodeficiencies, immunosuppression, idiopathic CD4 lymphocytopenia, malignancy and organ transplantation. Most patients with pneumocystis pneumonia will have the five findings of fever, cough, tachypnea, hypoxemia, and a high serum LDH. If the diagnosis is suspected, and an HIV test is negative, a CD4 lymphocyte count may be requested to see if this is low. The chest radiograph classically shows bilateral diffuse ground-glass infiltrates, which start at the perihilum, after which, these progress outwards.[50] Early in the AIDS era, the mortality rate for mechanically ventilated adults with pneumocystis pneumonia was 60-100%.[51] In a meta-analysis of risk factors for death for children under 5 years of age with acute lower respiratory infection in low to middle-income countries, a diagnosis of *Pneumocystis jirovecii* pneumonia had an odds ratio of 4.79 for death.[52]

There was one case of fatal *Rhizopus spp.* pneumonia identified through a lung biopsy in a child with acute myelogenous leukemia in relapse. The biopsy was done because of continued fever and a progressively worsening radiograph despite broad-spectrum antibacterial and antifungal treatment, and the patient did not survive. One non-immunocompromised patient had growth of *Candida spp.* from an ETA sample who recovered with anti-fungal treatment.

Determining the definite or likely (in resource-limited settings) etiology of childhood pneumonia is important for the clinician because treatment will vary considerably between organisms, although this paper purposely did not address specific treatments.

For many viral pneumonias, antimicrobials are not necessary, or available; these pneumonias may, however, be secondarily complicated by bacterial infections. For the different bacterial pneumonias, antibacterial choices may and will differ widely. For pneumocystis pneumonia, which is a life-threatening illness, antimicrobial treatment is different from the usual choices for pneumonia. For tuberculous pneumonia, anti-TB drugs are given. For some pneumonias (pneumocystis), corticosteroid treatment may be necessary or supportive oxygen therapy will more likely be required.

## CONCLUSION

In this 29-year retrospective study of childhood pneumonias in two private, urban, tertiary hospitals, an etiology was determined in 43%. Of those with a known etiology, *Mycoplasma pneumoniae* (11.9%), bronchiolitis (5.5%), *Mycobacterium tuberculosis* (5.2%), measles (4.8%) and *S. aureus* (4.2%) were the most common. The bacteremia rate was 6.3%. The data presented here mirrors the practice of one pediatric infectious disease doctor in two urban, private, tertiary hospitals where diagnostic and treatment options are readily available and utilized.

## LIMITATIONS OF THE STUDY

This study has several limitations. Not all pneumonia cases were referred to the author. There was a selection bias, as the milder pneumonias were generally managed by the general pediatricians while the ones which did not improve after two days or more, upon the discretion of the attending pediatrician, were referred to the infectious disease specialist and/or a pediatric pulmonologist. The author is not the sole pediatric infectious disease specialist in the two private hospitals included in this study.

Furthermore, there are several pediatric pulmonologists who see admitted patients with pneumonia. Lastly, the diagnostic procedures have greatly evolved in the last three decades when data collection was done.

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Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 55-63 July-December 2022
Malimban JG, Garcia RDJ and Francisco-Mallari MR. A Comparative Study of Pediatric Patients with Complete vs. Incomplete Kawasaki Disease in a Tertiary Hospital: An Eleven Year Review
https://doi.org/10.56964/pidspj20222302008

**ORIGINAL ARTICLE**

# A COMPARATIVE STUDY OF PEDIATRIC PATIENTS WITH COMPLETE VS. INCOMPLETE KAWASAKI DISEASE IN A TERTIARY HOSPITAL: AN ELEVEN YEAR REVIEW

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## ABSTRACT

**Introduction:** Kawasaki disease (KD) is the leading cause of acquired heart disease in childhood, but its diagnosis remains challenging since a significant number of cases do not meet the diagnostic criteria (Incomplete KD). This may delay the diagnosis and initiation of treatment, and increase the risk of morbidity from coronary artery complications.

**Objectives:** This study compared the clinical profile and treatment outcomes of children with complete and incomplete KD.

**Methods:** This is a cross-sectional, retrospective study of pediatric patients diagnosed with KD and admitted in a tertiary hospital from January 1, 2010 to December 31, 2020. Demographics, clinical manifestations, laboratories, 2D echocardiography (2DE) findings and treatment outcomes were obtained by review of medical records and analyzed using descriptive statistics.

**Results:** Among 135 patients studied, 71% were classified as Incomplete Kawasaki Disease. Majority (89%) were children more than 1 year old and predominantly male (55%). Five classic features, other than fever, were more frequent in complete KD - bilateral bulbar conjunctivitis, mucosal changes in the lip and oral cavity, polymorphous exanthem, changes in extremities, and cervical lymphadenopathy. Fever (100%), conjunctivitis (100%), rashes (97%) and oral changes (90%) were the most common findings in complete KD, while fever (100%), rashes (56%), conjunctivitis (46%) and oral changes (35%) were noted in incomplete KD. Higher CRP (167 mg/L vs. 100 mg/L) and lower albumin levels (30 g/L vs. 38 g/L) were seen in complete KD. Coronary artery dilatation (56% vs. 48%) was frequently detected in both complete and incomplete KD. Majority (96%) of cases received only one dose of IVIG and 4% needed additional treatment with methylprednisone.

**Conclusion:** The five principal features of KD other than fever, elevated CRP and lower albumin levels were significantly more common in complete cases. No significant differences in the demographics and 2DE findings of children with complete and incomplete KD were observed.

**KEYWORDS:** *Incomplete and Complete Kawasaki Disease, Acquired Heart Disease, Coronary Artery Dilatation and Aneurysms*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and that all authors have met the requirements for authorship.

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## INTRODUCTION

Kawasaki disease (KD) is an acute febrile vasculitis that predominantly affects medium-sized arteries, such as the coronaries.[1] It is the leading cause of acquired heart disease in childhood, especially in developed countries such as Japan and the US; however, the underlying etiology remains incompletely understood. Various studies postulated the development of the disease and its relation to the combined effects of an infectious trigger, immune response and genetic susceptibility.[2] Since its etiology remains elusive, no specific laboratory test has been developed to aid in confirming the disease, hence, diagnosis of KD is based on internationally accepted criteria. This includes fever lasting for ≥ 5 days, with at least four of the five principal features: bilateral bulbar conjunctival injection without exudates, changes affecting the lips and oral cavity (erythema, redness and cracking of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa), polymorphous exanthem, changes in peripheral extremities (erythema of palms and soles, edema of hands and feet and periungual peeling of fingers and toes) and cervical lymphadenopathy ≥ 15 $mm^3$.

A significant number of patients fail to meet the criteria. Patients with incomplete KD usually present with fever for more than 5 days, with two or three of the criteria for classic KD. Diagnosis of incomplete KD is based on the presence of 2D echocardiographic (2DE) findings suggestive of KD, such as coronary artery abnormalities complemented by laboratory results. In one study by McCrindle, *et al.*, the presence of more than three of the following laboratory findings, such as white blood count of ≥ 15,000 $mm^3$, platelet count of ≥ 450,000 $mm^3$, pyuria of 10 WBC/hpf, albumin of ≤3 g/dl, elevation of alanine aminotransferase (ALT) and anemia for age, support the diagnosis of KD.[3] Diagnosing a patient with incomplete KD is challenging, may lead to delays in treatment, and results in higher rates of cardiac complications.

Presence of coronary artery abnormalities, seen in about a quarter of patients who do not receive appropriate treatment, is an important complication of KD. This may lead to more severe sequelae, such as myocardial infarction and death, with the risk of mortality from coronary complications at approximately 2-3%.[3] Several studies prove that providing early treatment with high dose intravenous immunoglobulin (IVIG), combined with acetylsalicylic acid, leads to a lower incidence of coronary artery aneurysm; hence, this study compared the clinical profile and treatment outcomes of complete and incomplete KD to facilitate early recognition, diagnosis and management of the condition.[4]

## MATERIALS AND METHODS

This was a retrospective cross-sectional study involving pediatric patients less than 18 years old, admitted with a diagnosis of KD in a private, urban, tertiary hospital from January 1, 2010 to December 31, 2020. A minimum sample size of 170 (24 complete KD cases and 146 incomplete KD children) were required for this study based on a confidence interval of 95% and 5% margin of error. The proportion of complete and incomplete cases was taken from a previous study by Behmadi, *et al.*[5] However, on review of records, only a total of 135 pediatric patients were obtained, which was below the desired sample size; thus, a total census approach was utilized.

Upon approval by the hospital's Institutional Review Board (IRB), the medical charts of children diagnosed with KD were retrieved and reviewed via the electronic medical records (EMR) system and ArchiveOne database. Eligible exposed case participants were patients diagnosed with KD based on internationally accepted criteria.[3]

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Unexposed case participants were those who did not meet the criteria, but who had 2D echocardiographic findings suggestive of KD, such as coronary abnormalities, complemented by laboratory abnormalities, such as a peripheral white blood count (WBC) of ≥ 15,000 $mm^3$, platelet count of ≥ 450,000 $mm^3$, pyuria of ≥ 10 WBC/hpf, albumin of ≤ 3 g/dl, elevated alanine aminotransferase (ALT) and anemia for age. Excluded were those who did not receive the standard treatment for KD and those who were lost to follow up with no repeat 2DE results.

Descriptive statistics were used to present the clinical profile of eligible participants. Categorical variables were reported by frequency and proportion. Shapiro-Wilks test was used to determine the normality distribution, while Levene's test was used to test the homogeneity of variance of continuous variables. Continuous quantitative data that met the normality assumption was summarized using mean and standard deviation, while those that did not were described using median and range. Continuous variables that satisfied the dual assumption of normality and homogeneity were compared using independent t-test. The non-parametric Mann-Whitney U test was used for non-Gaussian variables. Categorical variables were compared using Chi-square test. If the expected percentages in the cells were less than 5%, Fisher's Exact test was used. Null hypothesis was rejected at 0.05 α-level of significance. STATA version 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

### Ethical Considerations

This study was conducted upon the approval of the hospital's Institutional Review Board (IRB). Since the study only required review of records with no direct interaction with eligible subjects, a waiver of informed consent was granted by the IRB. Data privacy and confidentiality were strictly preserved by anonymizing the case documents and results of the study.

## RESULTS

A total of 154 patient records were extracted but 19 were excluded for the following reasons: not given standard KD treatment (n=6); diagnosis other than KD – acute gastroenteritis, infective endocarditis, pneumonia (n=3); transfer of hospital or discharged against medical advice (n=2); and missing charts (n=19). A total of 135 patient records were included in this study.

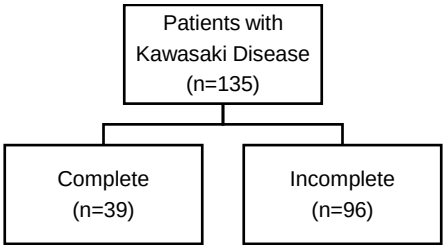


Table 1 presents the demographic profile of pediatric patients with KD. Only fifteen (11%) were less than 1 year old, with the rest falling in the 1-2 years (45%) or older age ranges (44%). Mean ages of patients with complete KD and incomplete KD were not significantly different. In terms of gender distribution, over half of patients (55%) were male with a 1.2:1 male to female ratio. A sibling history of KD was present in 2 patients. Age, sex, chief complaint and family history were comparable between the two groups.

Table 1. Demographic characteristics of pediatric patients with Kawasaki Disease

| Parameter | All (n=135) | Complete (n=39) | Incomplete (n=96) | *p* |
|---|---|---|---|---|
| | Frequency (%); Median (Range) | | | |
| Age, years | | | | .416* |
| <1 | 15 (11) | 2 (5) | 13 (14) | |
| 1–2 | 61 (45) | 19 (49) | 42 (44) | |
| >2 | 59 (44) | 18 (46) | 41 (43) | |
| Age (years, mean± SD) | 3.06 | 3.06 (±2.6) | 2.71 (±2.1) | .460‡ |
| Sex | | | | .197† |
| Male | 74 (55) | 18 (46) | 56 (58) | |
| Female | 61 (45) | 21 (54) | 40 (42) | |
| Family history of KD, siblings | 2 (1.5) | 1 (2.6) | 1 (1.0) | .496* |

Statistical tests used: * - Fisher's Exact test; † - Chi-square test; ‡ - Mann-Whitney U test

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Vol 23 No 2, pp. 55-63 July-December 2022
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https://doi.org/10.56964/pidspj20222302008

Table 2 compares the clinical characteristics of the two groups. Majority of patients presented with fever as the chief complaint in both complete (100%) and incomplete KD (91%). Children had fever for a median of 6 days (range 1 to 28) before consult and was not significantly different in frequency and duration between the two groups. Other than fever, five other presenting symptoms (bilateral bulbar conjunctivitis, changes in lip and oral cavity, polymorphous exanthem, changes in extremities, and cervical lymphadenopathy) were significantly more common in the complete KD group.

Table 2. Clinical characteristics of pediatric patients with Kawasaki Disease

| Characteristics | | All (n=135) | Complete (n=39) | Incomplete (n=96) | *p* |
|---|---|---|---|---|---|
| | | Frequency (%); Median (Range) | | | |
| Chief complaint | Fever | 126 (93) | 39 (100) | 87 (91) | |
| | Rash | 2 (1.5) | 0 (0) | 2 (2.1) | |
| | Changes in extremities | 1 (0.74) | 0 (0) | 1 (1.0) | |
| | Cervical lymphadenopathy | 2 (1.5) | 0 (0) | 2 (2.1) | |
| | Swelling | 3 (2.2) | 0 (0) | 3 (3.1) | |
| | Palpable mass | 1 (0.74) | 0 (0) | 1 (1.0) | |
| Duration of chief complaint, days | | 6 (1 – 28) | 7 (2 – 15) | 6 (1 – 28) | .329‡ |
| Presenting symptoms | Fever | 135 (100) | 39 (100) | 96 (100) | 1.0 |
| | Bilateral conjunctival injection without exudates | 83 (61) | 39 (100) | 44 (46) | **<.001**† |
| | Polymorphic exanthem | 92 (68) | 38 (97) | 54 (56) | **<.001**† |
| | Changes in lips and oral cavity | 69 (51) | 35 (90) | 34 (35) | **<.001**† |
| | Changes in extremities | 35 (26) | 23 (59) | 12 (13) | **<.001**† |
| | Cervical lymphadenopathy | 56 (41) | 30 (77) | 26 (27) | **<.001**† |

Statistical tests used: * - Fisher's Exact test; † - Chi-square test; ‡ - Mann-Whitney U test

Table 3 cites the other clinical features among pediatric patients with KD. Three patients in the complete KD group had cardiovascular findings, such as systolic murmurs and chest pain, the frequency of which was significantly more common in the complete KD group. The proportion of other non-specific symptoms - respiratory (cough and colds), gastrointestinal (vomiting and diarrhea), musculoskeletal (neck and joint pains) and others, such as throat pain and epistaxis, were not significantly different between the two groups.

Co-infections were seen in 27% of patients, most commonly pneumonia. Others were: urinary tract infections (7%), 3 culture confirmed *E. coli* and 7 culture negative UTI, upper respiratory tract infections (7%), and acute gastroenteritis (4%).

Table 3. Other clinical findings of pediatric patients with Kawasaki Disease

| Clinical Findings | All (n=135) | Complete (n=39) | Incomplete (n=96) | *p* |
|---|---|---|---|---|
| | Frequency (%); Median (Range) | | | |
| Cardiovascular | 3 (2) | 3 (8) | 0 (0) | **.023*** |
| Respiratory | 39 (29) | 7 (18) | 32 (33) | .074† |
| Gastrointestinal | 46 (34) | 15 (38) | 31 (32) | .490† |
| Musculoskeletal | 4 (3.) | 2 (5) | 2 (2) | .579* |
| Others | 9 (7) | 3 (8) | 6 (6) | .717* |
| With co-infection | 37 (27) | 7 (18) | 30 (31) | .116‡ |
| Pneumonia | 12 (9) | 4 (10) | 8 (8) | .360* |
| Urinary Tract Infection | 10 (7) | 2 (5) | 8 (8) | .460* |
| Acute Gastroenteritis | 5 (4) | - | 5 (5) | .176* |
| Upper Respiratory Tract Infection | 10 (7) | 1 (3) | 9 (9) | .157* |

Statistical tests used: * - Fisher's Exact test; † - Chi-square test; ‡ - Mann-Whitney U test

Laboratory profile of pediatric patients with KD showed that only the CRP level was significantly higher and the serum albumin was significantly lower in the complete KD group. The rest of the variables were not significantly different between the two groups.

Table 4. Laboratory profile of pediatric patients with Kawasaki disease

| Laboratory Parameter | All (n=135) | Complete (n=39) | Incomplete (n=96) | *p* |
|---|---|---|---|---|
| | Median (Range); Mean ± SD | | | |
| Hemoglobin | 11.6 (8.3–17.9); [n=131] | 11.9 (8.3–13.7); [n=38] | 11.5 (8.4–17.9); [n=93] | .531 |
| Hematocrit | 34.6 (24.8–49.7) | 36.2 (24.8–39.3) | 34 26.1–49.7) | .306 |
| White blood cell | 15.1 (2.7–34.7) | 15.1 (8.6–34.7) | 15 (2.7–32.1) | .944 |
| Platelet | 385 (167–905) | 372 (250–697) | 387 (167–905) | .664 |
| C-reactive Protein | 114 (1.4–364) | 167 (45–364) | 99 (1.4–347) | **.024** |
| ESR | 86 (1–140) | 111 (5–140) | 83 (1–130) | .958 |
| Serum sodium | 133.7 ± 3.9; [n=19] | 134.7 ± 2.6; [n=9] | 132.6 ± 4.8; [n=9] | .264§ |
| Albumin | 37.2 (26–46); [n=29] | 30 (26–43.6); [n=9] | 38 (27.4–46); [n=20] | **.006** |
| ALT (SGPT) | 39.7 (6–309.53); [n=60] | 64.0 (12–309.53); [n=16] | 33.8 (6–247.11); [n=44] | .072 |

Statistical tests used: If with section sign (§), Independent t-test. Otherwise, Mann-Whitney U test.

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As for the initial 2DE during admission, coronary artery dilatation was more common in the complete KD group (56% vs. 48%), but the difference was not statistically significant. Differences in other 2DE findings between the two groups were not significant.

Table 5. 2D Echocardiogram results of pediatric patients with Kawasaki disease on admission

| 2D Echocardiogram results | All (n=134) | Complete (n=39) | Incomplete (n=95) | *p* |
|---|---|---|---|---|
| | Frequency (%) | | | |
| Suggestive of KD | 100 (75) | 28 (72) | 72 (76) | .629 |
| **On admission** | | | | |
| Coronary Artery Aneurysm/ Dilatation | 68 (51) | 22 (56) | 46 (48) | .401 |
| Pericardial Effusion | 70 (52) | 18 (46) | 52 (55) | .366 |
| Perivascular Brightness of the Coronary Artery | 16 (12) | 2 (5) | 14 (15) | .150* |
| Left Ventricular Dysfunction | 27 (20) | 7 (18) | 20 (21) | .684 |

Statistical test used: If with asterisk (*), Fisher's Exact test. Otherwise, Chi-square test.

Only 62 of 135 patients (62%) had a follow-up 2DE six weeks from illness onset with no significant differences between the two groups. Further analysis revealed that out of 68 patients who had coronary artery dilatation on admission, 21 (7 complete KD and 14 incomplete KD) showed normal 2DE by the 6$^{th}$ week, while six (1 complete KD and 5 incomplete KD) had normal results beyond the 6$^{th}$ week of illness. Length of recovery based on 2DE findings varied from as short as 1 month to as long as 15 months.

All patients received one dose of IVIG, except for one who required a second dose due to disease recurrence after 2.3 years. Four patients (10%) in the complete KD group and two (4%) in the incomplete KD group required additional treatment with methylprednisone due to persistent fever despite IVIG treatment.

Children with incomplete KD had a significantly longer (6.8 vs. 5.9 days) hospital stay.

One patient in each of the groups had fever recurrence after one dose of IVIG. One of these received additional treatment with methylprednisone, while the other received another dose of IVIG.

Table 6. Treatment and outcome of patients

| Parameter | | All (n=135) | Complete (n=39) | Incomplete (n=96) | *p* |
|---|---|---|---|---|---|
| | | Frequency (%) | | | |
| Intravenous immuno-globulin | 1$^{st}$ dose | 135 (100) | 39 (100) | 96 (100) | - |
| | 2$^{nd}$ dose | 1 (0.74) | 1 (2.6) | 0 (0) | .289* |
| Methylprednisone | | 6 (4.44) | 4 (10.3) | 2 (4.1) | .058* |
| Treatment | IVIG alone | 129 (95.6) | 35 (89.7) | 94 (97.9) | .058* |
| | IVIG + 2nd dose of IVIG | 1 (0.74) | 1 (2.6) | 0 (0) | |
| | IVIG + Methylpred-nisone | 5 (3.70) | 3 (7.7) | 2 (2.1) | |
| Length of fever before treatment | | 8 (3–29) | 7 (3–14) | 8 (4–29) | **.018**‡ |
| Length of fever after treatment | Within 36 hours | 124 (91.9) | 36 (92.3) | 88 (91.7) | .999* |
| | More than 36 hours | 11 (8.1) | 3 (7.7) | 8 (8.3) | |
| Day of illness on admission | | | 6.77 (±2.5) | 6.80 (±4.0) | .3299 |
| Length of hospital stay | | | 5.92 (±3.7) | 6.77 (±3.8) | **.0042**‡ |
| Persistence of CAA | | 17 (12.6) | 2 (5.1) | 15 (15.6) | .151* |
| Recurrence | | 2 (1.5) | 1 (2.6) | 1 (1.04) | .496* |
| Additional treatment | | 2 (1.5) | 1 (2.6) | 1 (1.04) | .496* |

Statistical tests used: *–Fisher's Exact test; †–Chi-square test; ‡–Mann-Whitney U test.

## DISCUSSION

Timely diagnosis of Kawasaki Disease poses difficulties and challenges among pediatricians given the lack of a specific diagnostic test. Diagnosis depends on the presence of clinical criteria which may not be present all at the same time, which further contributes to delays. Early recognition of clinical, laboratory and echocardiographic findings that support the diagnosis of KD in a patient whose principal features do not meet clinical criteria, may not only result to timely diagnosis and initiation of appropriate treatment but may also limit the risk for coronary artery sequelae.

This retrospective study involving 135 children with KD compared the findings between complete vs. incomplete KD.

Patients affected in this study were children more than 1 year old, with a mean age of 3.1 (±2.6) years and 2.7 (±2.1) years for complete and incomplete KD, respectively. In this study, an older mean age for complete KD, although not significant, has also been reported, consistent with findings in other studies.[5-8] Younger children, particularly those aged six months and below, have been reported to present with incomplete and milder clinical features, making them prone to treatment delays and subsequent development of coronary artery abnormalities, hence the importance of considering KD in all infants with prolonged unexplained fever.[6-8] As to gender distribution, 55% of KD patients were male, similar to other local and foreign studies where male preponderance in both complete and incomplete KD has been reported.[5,9-11]

A family history of KD was reported in this study, with two siblings affected by the condition 2 years and 8 months apart. This is similar to a local study by Nable, *et al.* in 2002 on the profile of KD in children, where family history of KD was observed in nine percent of patients, with two siblings affected by the disease one month apart.[9] In another study by Fujita, *et al.*, the rate of the second-case of KD within a year after onset of the first case in a family was 2.1% for siblings, with a relative risk of approximately 10-fold compared to the general population. KD was diagnosed in half of the second cases within 10 days of the first case in the family.[12] Higher rates of the disease among children with family history of KD support the contribution of genetic factors in the susceptibility and etiology of the disease.

Co-infection was observed in 27% of patients, with pneumonia (9%) being most common in the two groups.

Several studies have postulated the association of infection with KD because of similar clinical presentations, marked seasonality, occurrence during epidemics, and a peak incidence among children 6 months to 2 years.[2] Chang, *et al.* found several viral agents, including enteroviruses, adenoviruses, human rhinovirus and coronavirus, isolated from KD patients during the acute course of illness.[13] Moreover, *Staphylococcus aureus*, *Streptococcus pyogenes* and *Mycoplasma pneumoniae* have also been identified.[2] In a recent systematic review by Goncalves, *et al.*, the COVID-19 pandemic resulted in a significant increase in the incidence of KD which suggests an association between COVID-19 and KD, especially the severe type.[14] Despite several studies attempting to define the etiopathogenesis of KD, no specific etiology has been identified and KD is believed to result from the combined effects of infectious agents, the host's immune response and a genetic susceptibility, which likely contribute to the development of the disease.[2]

Several studies reported the prevalence of incomplete KD to be from 15 to 36%.[6] Contrary to other studies, our study reported a higher incidence of KD with incomplete presentation (71%) at the time of diagnosis. Fever was the most common initial symptom, lasting an average of 6.8 and 6.9 days for complete and incomplete KD groups, respectively. Similar to previous studies, five principal features, apart from fever, were significantly more common in the complete KD group. Among the principal features, bilateral conjunctival injection without exudates, polymorphic exanthem and oral changes were the most common symptoms in both groups. Consistent with previous studies by Behmadi, *et al.*, Perrin, *et al.*, Manlhiot, *et al.*, Gorczyca, *et al.* and Giannouli, *et al.*, conjunctivitis, oral changes and rashes were most commonly seen in both complete and incomplete KD cases, and the frequency by which these were seen were higher in complete KD patients.[5,15-18]

However, in one study by Maric, *et al.*, these three clinical manifestations were found to be more frequent in the incomplete KD group.[19] Although the proportion of principal features were higher in the complete KD group, the clinical presentation of incomplete KD closely resembled that of complete KD. A high index of suspicion for KD is warranted in patients presenting with persistent fever accompanied by bilateral conjunctival injection without exudates, polymorphic exanthem and oral changes. Earlier studies also reported a longer interval between symptom onset and diagnosis in KD patients with incomplete presentation.[14] Incomplete KD in this study took one day longer between symptom onset and diagnosis, which also reflects the time required to rule out other diagnostic considerations.

Respiratory (cough and colds), gastrointestinal (vomiting and diarrhea), musculoskeletal (neck and joint pains) and other nonspecific symptoms (throat pain and epistaxis) were similar in frequency for both groups. However, cardiovascular manifestations (systolic murmurs and chest pain) were more common in the complete KD group, which may result from inflammation of the coronary arteries, pericardium, myocardium and endocardium, including the valves. In this study, two of the three patients with cardiac manifestations had valvular regurgitation (tricuspid valve) on 2DE. Valvular dysfunction may be seen in approximately 25% of patients which has been postulated to result from the same inflammatory mechanism as with other KD changes during the acute phase of the disease.[3] Cardiac symptoms are not common in KD patients even in those with severe coronary artery abnormalities (giant aneurysm) except when severe coronary artery flow disturbances or thromboses are present, resulting to myocardial ischemia; thus, children with cardiac manifestations should be closely monitored for the development of myocardial ischemia and infarction.[3]

As for laboratory findings, CRP was higher and albumin levels were lower in complete KD than incomplete KD. Several studies have identified CRP elevation and hypoalbuminemia as risk factors for coronary artery aneurysms and resistance to IVIG treatment.[16,18] These features may reflect disease severity and thus, require prompt echocardiographic assessment and initiation of treatment. Other laboratory features, such as anemia, leukocytosis, thrombocytosis, elevated ESR, elevated ALT and hyponatremia, were not significantly different between the two groups. Behmadi, *et al.* reported CRP and albumin levels as not significantly different between the two groups but found that hyponatremia and elevated alanine aminotransferase (ALT) to be more common in the complete KD group, while anemia and thrombocytosis were more common in the incomplete group.[5] Similar laboratory features in this study are shared by the two groups. Absence of a differentiating laboratory feature in this study contributes to the difficulty in identifying an appropriate diagnostic marker that can be used to assist in the diagnosis of the disease.

Previous studies, including the one by Perrin, *et al.*, documented that coronary artery abnormalities were more common in those with incomplete KD.[15] However, this study did not find any differences in the incidence of CAA between the two groups similar to Manlhiot, *et al.*[16] Behmadi, *et al.* also found no significant differences in the rates of coronary artery dilatation and aneurysms, myocarditis, valvular lesions, pericardial effusion and perivascular brightness between complete and incomplete KD patients; however, ectasia and lack of tapering of the distal coronary vessels were more frequent in the incomplete group.[5] In this study, coronary artery dilatation/aneurysm (51%) was the most common abnormality in the two groups, while perivascular brightness of the coronary artery (12%) was the least noted finding.

Short and long term coronary outcomes were similar among patients with complete and incomplete Kawasaki disease, consistent with the study by Shilvalingham, *et al.*[20]

Patients in both groups were treated with IVIG within the optimal time of 7-10 days of illness, which may have prevented the development of CAA and explained the similarities in the incidence of CAA between the two groups. It also suggests an increased awareness of the disease. A higher incidence of CAA in incomplete KD in most published studies may reflect a diagnostic bias because 2DE is required to support the diagnosis or may lead to underestimation of incomplete KD without 2DE findings of CAA.[15]

Given the similarities between the two groups, it is often the combination of clinical features, laboratory findings and 2DE results which prompt the clinician to label the case as incomplete KD. The high incidence of incomplete KD in this study showed that clinicians had a high index of suspicion of the disease and were able to recognize KD with incomplete presentation despite fewer clinical manifestations and lack of useful laboratory markers that differentiate complete vs. incomplete KD. This study was not able to meet the minimum sample size and was limited by the number of patients with follow up 2DE results, hence, a larger number of patients is recommended for futures studies.

## CONCLUSION

This study found that five principal features of KD (conjunctival injection, rash, oral changes, extremity changes and cervical lymphadenopathy), elevated CRP and lower albumin levels were significantly more common in complete than incomplete KD. However, the demographic and other clinical features, laboratory and 2DE findings were similar between the two groups.

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Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 64-70 July-December 2022
Roble KNB and Tagocon RA. Mean Hematocrit Values, Disease Severity, and Discharge Status of Undernourished Versus Well-Nourished Children with Dengue Infection in a Tertiary Government Hospital
https://doi.org/10.56964/pidspj20222302009

**ORIGINAL ARTICLE**

# MEAN HEMATOCRIT VALUES, DISEASE SEVERITY, AND DISCHARGE STATUS OF UNDERNOURISHED VERSUS WELL-NOURISHED CHILDREN WITH DENGUE INFECTION IN A TERTIARY GOVERNMENT HOSPITAL

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## ABSTRACT

**Background:** Studies comparing hematocrit values, disease severity, and discharge status between well-nourished and undernourished pediatric dengue patients are limited.

**Objective:** This study compared the mean hematocrit values, disease severity and discharge status of undernourished vs. well-nourished pediatric dengue patients admitted in a tertiary government hospital.

**Methodology:** A retrospective cohort study involving 114 pediatric dengue patients, with comparison groups of well-nourished and undernourished children matched according to age, phase of illness and sex was done. Main outcomes measured were mean hematocrit values, disease severity and discharge status.

**Results:** There was a significantly lower mean pre-resuscitation hematocrit in the wasted (M=39.67%, SD=3.78) compared to the well-nourished group (M=43.68%, SD=4.72), p=0.006, among children >6 to 12 years old in the febrile phase. There were no significant differences in disease severity and discharge status between wasted and well-nourished children. In those >2 to 6 years old in the febrile phase, the severely wasted had significantly higher pre-resuscitation hematocrit (M=43.28%, SD=4.77) compared to well-nourished children (M=39.11%, SD=5.34), p=0.041. More severe dengue, worse discharge status and an earlier time to demise was seen among severely wasted children.

**Conclusion:** Wasted participants had significantly lower mean hematocrit values with no difference in disease severity and discharge status when compared to well-nourished participants. Severely wasted children had significantly higher hematocrit values, severe dengue, and worse discharge status.

**KEYWORDS:** *Dengue Fever, Undernutrition, Hematocrit*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and that all authors have met the requirements for authorship.

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 64-70 July-December 2022
Roble KNB and Tagocon RA. Mean Hematocrit Values, Disease Severity, and Discharge Status of Undernourished Versus Well-Nourished Children with Dengue Infection in a Tertiary Government Hospital
https://doi.org/10.56964/pidspj20222302009

## INTRODUCTION

The World Health Organization reported in 2018 that 50 to 100 million dengue cases occur annually worldwide.[1] In the Philippines, as of 2019, dengue is the 2nd leading cause of death and 6th most common cause of mortality among communicable diseases in the 5 to 14 year age group.[2] In August of the same year, the Department of Health declared a national dengue epidemic in the country; and in the institution where this study was conducted, there was a noted increase of pediatric dengue cases in 2019 from 1,549 to 1,803, with a case fatality rate of 2.9%.[3-4]

Since dengue is a vector-borne systemic viral disease with a wide clinical spectrum ranging from mild flu-like symptoms to more severe manifestations (including persistent vomiting, severe abdominal pain and hypotension), early detection is crucial to management.[5-6] Laboratory tests to establish the diagnosis include detection of viral nucleic acid, antigens and antibodies. In areas with limited resources, clinicians rely on clinical manifestations and hematologic findings of decreasing platelet with concomitant rise in hematocrit.[6]

A local study done by Lim, Gatchalian and Capeding on two-hundred dengue patients aged 0 to 19 years old and admitted at the Research Institute for Tropical Medicine from 2000-2004 showed hematocrit values to have ranged from 29 to 64% (M=42%, SD=5).[7] The subjects included were admitted between one to ten days from start of clinical symptoms, however, nutritional status as well as timing of hematocrit determination were not identified. An elevated hematocrit for age or a rise of at least 20% from baseline warrants immediate attention, thus hematocrit monitoring plays an essential role in dengue management.[6]

Undernutrition is known to decrease hematocrit levels.

A study done by Gebreegziabiher, *et al.* revealed that anemia is generally more common in children who are wasted and severely wasted, and hemoglobin levels of undernourished children were relatively lower compared to those who are well-nourished.[8] Another study by Arya, *et al.* showed that about 95% of children aged 6 months to 5 years old with severe acute malnutrition had anemia with a mean hemoglobin level of 7.17 $\pm$ 2.26 gm/dL and a mean hematocrit level of 21.27 $\pm$ 6.63%.[9] Their healthy counterparts, on the other hand, had a mean hemoglobin level of 9.22 $\pm$ 3.362 gm/dL and a mean hematocrit level of 27.40 $\pm$ 8.98%. Although hematocrit levels were compared between undernourished and well-nourished participants, patients in both studies did not have dengue infection.

Mogra, *et al*. looked into the hematologic profile of 100 dengue patients - 8% of whom are severely wasted and 28% moderately wasted. All patients with severe dengue had hemoconcentration compared to only 70% in those with dengue with warning signs. This supports reviews that hemoconcentration is a prognostic factor for disease severity. The study, however, did not look into the effect of nutritional status on hematocrit levels and disease severity.[10] In another study of 4,532 dengue cases in Thailand from 1995 to 1999, a look into the nutritional status of participants revealed that 65 to 67% were well-nourished, 9 to 11% had moderate to severe malnutrition and 23 to 24% were overweight or obese.[11] The clinical signs, symptoms and laboratory findings were almost the same between the malnourished and those with normal nutritional status. However, about 37.8% of wasted and severely wasted patients developed shock compared to those with normal nutritional status where only 29.9% presented with shock. Moreover, a greater number of mortalities were identified in the malnourished group compared to those with normal nutritional status with a case fatality rate of 0.5% and 0.07%, respectively.

This contrasts with the 2020 study of Maneerattanasak and Suwanbamrung where undernutrition did not pose a greater risk of having severe type of dengue, although it appeared as a protective factor against dengue hemorrhagic fever and dengue shock syndrome. Only overweight and obese patients were found to have a higher risk in developing severe type of dengue infection.[12]

To date, there have been several studies done on undernutrition and dengue infection, but the effects of the former on mean hematocrit values, dengue disease severity and discharge status have not been explored. Hence, this study determined and compared pre-resuscitation hematocrit values, disease severity and discharge status between undernourished versus well-nourished pediatric dengue in-patients.

## MATERIALS AND METHODS

### Study Design

This is a retrospective cohort study approved by the Ethics Review Committee of the Education, Training, and Research Board. Outcomes assessed were hematocrit values, disease severity (dengue with warning signs or dengue severe) and discharge status (improved or expired) of the exposed group (those with undernutrition) and the unexposed group (those who are well-nourished).

### Study Population and Setting

Included were patients aged 0-17 years old admitted for the first time in a tertiary government referral and training hospital from January 1 to December 31, 2019 with a final diagnosis of dengue with warning signs or dengue severe, with documented hematocrit levels prior to any fluid resuscitation.

Excluded were overweight and obese patients as they have significantly higher hematocrit values and a more severe type of dengue;[13] patients referred from other institutions who received intravenous fluid resuscitation before baseline hematocrit determination; and patients with other known co-morbidities such as hematologic, renal, cardiac disease or concomitant bacterial infections as these conditions naturally alter the hemogram. Subjects who presented with severe bleeding and those needing blood transfusion at the time of hematocrit determination were also excluded.

### Methodology

Review of medical records was done and patients with a final diagnosis of dengue with warning signs or dengue severe from January to December 2019 were identified using the master list provided by the Medical Records Section. Cases were grouped according to nutritional status using the height and weight on admission and assessed based on the World Health Organization growth charts 2007.[14] Wasted and severely wasted patients were identified and sampled consecutively. Data on hematocrit value, age, sex, phase of illness, disease severity and discharge status were collected. For expired patients, time to demise was determined and categorized as expired less than or more than 48 hours from admission. Well-nourished dengue patients were also identified, sampled consecutively and matched with the undernourished group based on age, sex and phase of illness to control for confounding variables. Patients were grouped into the following age categories: >2 to 6 years old, >6 to 12 years old, and >12 to 17 years old. These age clusters were used as there are set hematocrit values per age category. Patients were also matched according to sex for the >12 to 17-year-old age group since there is a difference in the normal hematocrit values between sexes.[15]

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Lastly, patients were matched according to phase of illness since a rise in hematocrit is more evident during the critical phase due to plasma leakage.

**Sample Size**

Based on the study of Kalayanarooj and Nimmannitya, the sample size was calculated using the difference of two proportions formula, with a hypothetical proportion of 10% undernourished patients with dengue infection and 66% well-nourished patients with dengue infection, with 95% confidence interval.[11] A sample size of at least 15 participants per subgroup was calculated. We included 114 patient records, with 57 well-nourished and 57 undernourished (36 wasted and 21 severely wasted) patients, which is more than the sample size calculated.[16]

**Statistical Analysis**

Data were analyzed using the software SPSS. Descriptive studies were used to analyze demographic data. Independent samples T-test was used to compare the mean hematocrit values of well-nourished and undernourished patients. Chi-square was used to compare differences in disease severity and discharge status between groups and time to demise was analyzed using Fisher's Exact Test.

**RESULTS**

A total of 1,803 pediatric dengue cases were recorded in the hospital for 2019, however only 114 subjects were included and reviewed by consecutive sampling due to the rigorous matching process. As seen in Table 1, half (N=57, 50%) were identified as well-nourished and the rest (N=57, 50%) were classified as undernourished. The latter group was further classified into wasted (36) and severely wasted (21).

Matched well-nourished and wasted patients were mostly males (N=43, 59.7%), >6 to 12-year-olds (N=46, 63.9%), residing within Cagayan de Oro City (N=46, 63.9%), referred from other institutions (N=40, 55.6%) and were in the febrile phase of illness (N=54, 75%) at the time hematocrit values were obtained. As for matched well-nourished and severely wasted patients, an equal number of males and females were observed, majority were in the >2 to 6 years old age group (N=20, 47.6%) and residing outside the city (N=22, 52.4%). When comparing matched well-nourished and severely wasted subjects, 17 of 21 well-nourished patients were walk-ins (N=17, 81%). In contrast, those who were severely wasted were referrals from other institutions (N=14, 66.7%). Majority of subjects were in the febrile phase (N=40, 95.2%) when hematocrit values were obtained.

Table 1. Nutritional Status and Sociodemographic Profile of Patients with Dengue Infection

| Parameter | Well-nourished | Wasted | Total | | Well-nourished | Severely Wasted | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | N | N | Percentage (%) | N | N | N | Percentage (%) |
| Gender | | | | | | | | |
| Male | 22 | 21 | 43 | 59.7% | 12 | 9 | 21 | 50% |
| Female | 14 | 15 | 29 | 40.3% | 9 | 12 | 21 | 50% |
| Age group | | | | | | | | |
| >2 to 6 years old | 9 | 9 | 18 | 25% | 10 | 10 | 20 | 47.6% |
| >6 to 12 years old | 23 | 23 | 46 | 63.9% | 9 | 9 | 18 | 42.9% |
| >12 to 17 years old | 4 | 4 | 8 | 11.1% | 2 | 2 | 4 | 9.5% |
| Address | | | | | | | | |
| Within CDO | 25 | 21 | 46 | 63.9% | 10 | 10 | 20 | 47.6% |
| Outside CDO | 11 | 15 | 26 | 36.1% | 11 | 11 | 22 | 52.4% |
| Source | | | | | | | | |
| Walk-in | 15 | 17 | 32 | 44.4% | 17 | 7 | 24 | 57.1% |
| Referral | 21 | 19 | 40 | 55.6% | 4 | 14 | 18 | 42.9% |
| Phase of Illness | | | | | | | | |
| Febrile phase | 27 | 27 | 54 | 75% | 20 | 20 | 40 | 95.2% |
| Critical phase | 9 | 9 | 18 | 25% | 1 | 1 | 2 | 4.8% |

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Table 2 shows that there is a statistically significant difference in mean hematocrit values between well-nourished and wasted patients among those >6 to 12 years of age in the febrile phase, with wasted patients having a lower mean hematocrit (M=39.67%, SD=3.78) compared to well-nourished patients (M=43.68%, SD=4.72), p=0.006. When comparing well-nourished and severely wasted patients in the febrile phase, there is a statistically significant difference in mean hematocrit among patients >2 to 6 years of age, with the severely wasted having higher hematocrit levels (M=43.28%, SD=4.77) compared to well-nourished patients (M=39.11%, SD=5.34), p=0.041. Comparison between mean pre-resuscitation hematocrit values of well-nourished versus wasted patients, as well as well-nourished versus severely wasted patients, is seen in Table 2.

Table 2. Mean Hematocrit Values between Well-nourished vs. Wasted and Severely Wasted Pediatric Dengue Patients

| Phase of illness | Age group | Mean and Standard Deviation of Hematocrit Values (%) | | P-value | Mean and Standard Deviation of Hematocrit Values (%) | | P-value |
|---|---|---|---|---|---|---|---|
| | | Well-nourished | Wasted | | Well-nourished | Severely Wasted | |
| Febrile phase | >2 to 6 years old | 37.8 ± 4.30 | 37.64 ± 3.00 | 0.466 | 39.11 ± 5.34 | 43.28 ± 4.77 | 0.041 |
| | >6 to 12 years old | 43.68 ± 4.72 | 39.67 ± 3.78 | 0.006 | 38.99 ± 2.08 | 39.90 ± 3.35 | 0.262 |
| | >12 to 17 years old<br>Male<br>Female | 46.9 ± 7.14<br>44 | 44.87 ± 7.01<br>41.9 | 0.301<br>n/a | 40.10 ± 1.27<br>- | 40.35 ± 0.49<br>- | 0.410 |
| Critical Phase | >2 to 6 years old | 34 | 34.5 | n/a | - | - | - |
| | >6 to 12 years old | 38 ± 8.62 | 36.7 ± 3.67 | 0.431 | 41 | 53.2 | n/a |
| | >12 to 17 years old<br>Male | 40.3 | 43.5 | n/a | - | - | - |

Table 3 shows that 17 of 36 wasted patients were diagnosed with dengue with warning signs and 19 were diagnosed with dengue severe. On the other hand, half (50%) of well-nourished patients had dengue with warning signs and the other half had dengue severe.

Of the twenty-one severely wasted patients with dengue infection, six had dengue with warning signs and majority (N=15) had dengue severe. In contrast, majority (N=16) of the well-nourished were diagnosed with dengue with warning signs and only five were diagnosed with dengue severe. As to association between nutritional status and disease severity, there was no significant difference between the wasted and their matched well-nourished counterparts with a p-value of 0.814, but a significant difference was seen between the severely wasted and their well-nourished counterparts, p=0.02.

Table 3. Association between Nutritional Status and Disease Severity among Pediatric Dengue Patients

| Disease Severity | Nutritional Status (N) | | P-value | Nutritional Status(N) | | P-value |
|---|---|---|---|---|---|---|
| | Well-nourished | Wasted | | Well-nourished | Severely Wasted | |
| Dengue with Warning signs | 18 | 17 | 0.814 | 16 | 6 | 0.02 |
| Dengue Severe | 18 | 19 | | 5 | 15 | |
| Total | 36 | 36 | | 21 | 21 | |

Table 4 shows that there is no significant difference in discharge status between wasted patients and their matched well-nourished counterparts, p=0.326. However, there is a significant difference in discharge status when comparing severely wasted patients with those with normal nutritional status, with eleven (52.4%) severely wasted being discharged improved while ten expired (47.6%), in contrast to matched well-nourished patients who were all discharged improved, p <0.001. Among those who expired, there is no significant difference in time to demise from admission when comparing the wasted group compared to their well-nourished counterparts, p= 0.348. However, there was a significant difference between severely wasted patients compared to their well-nourished counterparts, with eight severely wasted patients expiring with only less than 48 hours of hospital stay, p <0.001.

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All ten severely wasted patients who expired were referrals from other institutions and were managed for more than 4 hours before transfer. Time to demise in this study only included the number of hours the subjects stayed in the hospital where the study was conducted.

Table 4. Association between Nutritional Status and Discharge Status among Pediatric Dengue Patients

| Parameter | | Nutritional Status (N) | | P-value | Nutritional Status (N) | | P-value |
|---|---|---|---|---|---|---|---|
| | | Well-nourished | Wasted | | Well-nourished | Severely Wasted | |
| Discharge Status | Improved | 32 | 29 | 0.326 | 21 | 11 | <0.001 |
| | Expired | 4 | 7 | | 0 | 10 | |
| Time to Demise of Expired Patients | <48 hours | 1 | 4 | 0.348 | 0 | 8 | <0.001 |
| | >48 hours | 3 | 3 | | 0 | 2 | |

## DISCUSSION

When comparing the wasted population and their well-nourished counterparts, no significant differences in disease severity and discharge status were seen in this study. This is consistent with the study of Maneerattanasak and Suwanbamrung which showed that children who developed dengue hemorrhagic fever were less likely undernourished than were healthy controls. This finding support theories that undernutrition is associated with a dysfunction of the innate and adaptive immune system, thus hindering an exaggerated host immune response, which plays a pivotal role in the pathogenesis of severe dengue.[12] This is contrary to the study of Kalayanarooj and Nimmannitya in Thailand, which showed that when malnourished patients contracted dengue fever, they presented with severe disease, had a higher risk of developing shock and had higher case fatality rates.[11] However, this study did not sub-categorize malnutrition into wasting and severe wasting.[11]

Gebreegziabiher, *et al.* noted that baseline hemoglobin and hematocrit levels of undernourished children were significantly lower compared to their well-nourished counterparts.[8] However, it does not follow that they will have a lower percentage rise in hematocrit when they develop dengue fever. In our study, it was shown that >2 to 6 years old severely wasted children with dengue had significantly higher mean hematocrit values compared to their well-nourished counterparts. Hemoconcentration among the severely wasted may be a sign of rapid deterioration. This study also showed that more severe disease and worse clinical outcomes are significantly associated with the severely wasted, but not the wasted population. More severely wasted patients developed shock, deteriorated and eventually expired. These findings were consistent with those of Kalayanarooj and Nimmannitya, where malnourished patients had a greater risk of developing dengue shock syndrome with a higher case fatality rate. These were attributed to the smaller extra-cellular and plasma volumes of undernourished children, thus shock develops more rapidly even with a lesser degree of plasma leakage.[11] Given this hypothesis, physicians should closely monitor severely wasted children for early signs of severe disease.

There were several limitations encountered in our study as follows: It was retrospective in nature and was done in a single-center, thus findings cannot be generalizable to the population at large. The gold standard for the diagnosis of dengue fever was not available for use in our study, and since there were participants who were referrals from other institutions with documented pre-resuscitation hematocrit values, not one machine was used in hematocrit determination. This in turn could have been affected by machine calibration. Association of hematocrit values with disease severity and discharge status was also not done.

In an attempt to control for confounding variables, there were age groups with only one subject per subgroup, thus significant differences in hematocrit values cannot be established. Lastly, a substantial number of participants were not included due to limitations in the matching process.

Further studies are recommended with the inclusion of a control group with more participants to be able to establish hematocrit values among Filipino children with dengue with varying nutritional status.

## CONCLUSION

Wasted participants had significantly lower mean hematocrit values with no difference in disease severity and discharge status when compared to well-nourished participants. Severely wasted children had significantly higher hematocrit values with severe dengue and worse discharge status.

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https://doi.org/10.56964/pidspj20222302010

**ORIGINAL ARTICLE**

# DIAGNOSTIC ACCURACY OF THE NEONATAL EARLY ONSET SEPSIS CALCULATOR IN SCREENING FOR EARLY ONSET SEPSIS IN NEONATES MORE THAN 35 WEEKS AGE OF GESTATION

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## ABSTRACT

**Background:** Early-onset sepsis (EOS) is a leading cause of morbidity and mortality among neonates. Diagnosis of EOS can be difficult as clinical signs are subtle. The use of the Neonatal EOS Calculator (NEOSC) may help screen high-risk neonates for EOS and may result in a significant reduction in unnecessary antibiotic use.

**Objective:** To determine the diagnostic accuracy of the NEOSC in screening for EOS in neonates more than 35 weeks age of gestation.

**Methodology:** This was a retrospective, case-control study where 245 septic (cases) and 245 non-septic (controls) neonatal and maternal medical records were reviewed. The EOS risk classification from the NEOSC was compared with the actual clinical outcome. An online statistical software (*medcalc*.org) was used to compute for the sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and accuracy of the NEOSC.

**Results:** Based on the NEOSC, only 64 of 245 clinically septic neonates were truly positive for sepsis while 181 were falsely negative for sepsis. Of the 245 non-septic neonates, 3 were falsely positive for sepsis, while 242 were truly negative for sepsis. With a 95% confidence interval, the computed variables showed a Sn 26.12%, Sp 98.78%, PPV 76.12%, NPV 89.95%, PLR 21.33, and NLR 0.75. The accuracy of the NEOSC is 89.33%.

**Conclusion:** The NEOSC had poor sensitivity and is not recommended in screening for EOS in neonates more than 35 weeks age of gestation. It may be used as an adjunct in EOS diagnosis due to its high specificity and accuracy.

**KEYWORDS:** *Neonatal Early Onset Sepsis, Neonatal sepsis, Sepsis (EOS) Calculator*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and that all authors have met the requirements for authorship.

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## INTRODUCTION

Early-onset sepsis (EOS) is a leading cause of morbidity and mortality among neonates. The World Health Organization (WHO) data in 2016 showed that 46% of global deaths among children under 5 years of age were neonatal deaths. In the Philippines, it accounts for 18% of all causes of death.[1]

Physicians are confronted with the need to identify neonates at highest risk of infection as clinical signs of EOS are nonspecific and variable. Blood culture is considered the gold standard for diagnosis of EOS, however, only less than 1% of neonates are culture positive, with the incidence of culture-proven EOS in newborns ranging between 0.5 to 1.2 cases per thousand live births. [2-3] Due to the low incidence of culture-proven EOS but potentially high-mortality rates, EOS is frequently diagnosed based on clinical presentation.[2]

The Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) published guidelines that have been utilized by clinicians for the management of EOS. These recommend empiric antibiotic initiation for all neonates who appear to be clinically ill at birth or are born to women diagnosed with chorioamnionitis.[4] Empiric treatment of newborns at risk or with suspected EOS represents the main contributor to the use of antibiotics in early life. Unnecessary evaluations and antibiotic treatment are, however, not risk-free. Newborns are often admitted to a neonatal intensive care unit (NICU) which may interrupt parental bonding and breastfeeding. Moreover, long-term detrimental effects have been linked to antibiotic exposure which include alteration of the neonatal microbiome, asthma, inflammatory bowel disease, autoimmune disease, antibiotic resistance and mortality.[2] Optimizing antibiotic use in neonates is critical as they are vulnerable to their adverse effects.

Factors that increase the risk for infection include maternal Group B *Streptococcus* (GBS) colonization, maternal fever, chorioamnionitis, prolonged rupture of membranes (>18 hours) and inadequate intrapartum antibiotic administration before delivery.[5]

An online calculator known as the Neonatal Early Onset Sepsis Calculator (NEOSC) is a multivariate prediction model that could be used to predict the probability of EOS based on five objective maternal risk factors available at the time of birth.[6] Previous studies about the efficacy of the NEOSC was associated with reduced usage of antibiotics (from 6% to 1.4%), laboratory tests (from 15.5% to 2.5%) and admissions to neonatal units (from 19.1% to 5.4%).[7] Although this tool may serve to decrease unnecessary antibiotic treatment, its diagnostic accuracy has yet to be determined.

## MATERIALS AND METHODS

### Study Design

This was a retrospective case-control study where clinical outcomes of septic neonates (cases) and non-septic neonates (controls) were reviewed and compared with their classification in the NEOSC.

### Study Setting

The study was conducted in a tertiary private hospital.

### Study Population

Neonates more than 35 weeks of age of gestation (AOG) born at a tertiary private hospital from January 2019 up to March 2021 and admitted for at least 72 hours were included in the study.

#### *Septic Neonates (Cases)*

Septic neonates are neonates whose clinical course and final diagnosis on discharge are consistent with EOS as defined by the *Standards of Newborn Care.*[5]

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These cases presented as systemic inflammatory response syndrome (SIRS) secondary to infection occurring within 72 hours after birth. SIRS included the presence of 2 or more of the following: fever or hypothermia (>37.5˚C or <36.5˚C), tachycardia (HR ≥160bpm), tachypnea (RR ≥60cpm), an abnormally high or low white blood cell count (≤9 x $10^9$ cells/L) and or elevated CRP (≥1.59 mg/dL) and isolation of a pathogen from blood culture, lumbar puncture or tracheal aspirate obtained immediately after endotracheal tube placement. Those with severe congenital malformations requiring surgical intervention and with concomitant diagnosis of Respiratory Distress Syndrome, Neonatal Pneumonia and Meconium Aspiration Syndrome were not included in the study.

***Non-Septic Neonates (Control)***

Non-septic neonates are neonates whose clinical course and final diagnosis on discharge are not consistent with EOS as defined by the *Standards of Newborn Care*.[5] These cases were clinically well with no persistent physiologic abnormalities recorded in the vital signs monitoring sheet (temperature, respiratory rate and heart rate) and with unremarkable laboratory results.

**Scope and Limitations**

The population was limited only to newborns at least 35 weeks AOG from a single tertiary institution who were admitted for EOS between January 2019 and March 2021. Data was gathered by review of maternal and neonatal medical records.

The prevalence rate of EOS in a particular setting would affect the statistical analysis used to compute the positive and negative predictive values as well as accuracy. A case-control study design was performed for this initial study as this was less invasive for a susceptible population such as neonates.

**Data Collection and Analysis**

After study approval by the Hospital Institutional Review Board (IRB), data collection commenced and was based on medical chart review. A master list of all neonates was taken from the hospital's Information Technology Service Team and a total of 245 records of septic neonates and 245 records of non-septic neonates were retrieved together with maternal medical records. Two research assistants (RA) were trained to collect the data. Each RA was assigned a specific list where each neonate had a corresponding unique patient number to maintain anonymity and avoid duplication. The neonatal outcome was obtained, as well as the temperature, heart rate, respiratory rate, and specific laboratory data (complete blood cell count, CRP and presence or absence of blood culture or CSF culture). The classification whether the neonate is septic or non-septic was based on the clinical course, laboratory results and diagnosis upon discharge and were verified by a neonatologist based on the definition of EOS in the *Standards of Newborn Care*.[5]

The following variables were entered into the NEOSC: AOG, highest maternal temperature during labor, duration of membrane rupture before delivery, GBS status at birth and intrapartum antibiotic treatment including the length of time before delivery. An incidence of 0.5 per 1000 live births (which is the CDC national incidence rate) was used as no local incidence rate was available. Based on the color code and clinical recommendation from the NEOSC, a *green* recommendation *(no culture and no antibiotics with routine vitals)* was considered negative for neonatal sepsis (nEOScalc) while those with *yellow* recommendation *(blood culture with vital signs every 4 hours every 24 hours)* and *red* recommendation *(empiric antibiotics with vitals per NICU recommendations*) were considered positive for neonatal sepsis (pEOScalc). Calculator scores whether a neonate was nEOScalc or pEOScalc from the NEOSC were noted and compared with the actual clinical outcome.

Pediatric Infectious Disease Society of the Philippines Journal
Vol 23 No 2, pp. 71-78 July-December 2022
Del Carmen KJC, Du ALM and Kimseng KJN. Diagnostic Accuracy of the Neonatal Early Onset Sepsis Calculator in Screening for Early Onset Sepsis in Neonates More Than 35 Weeks Age of Gestation
https://doi.org/10.56964/pidspj20222302010

An online statistical software *(www.medcalc.org)* was used to compute for the sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, and accuracy of the NEOSC.[8] A five-year (2016-2021) local prevalence of EOS in the study setting was computed and subsequently used in computing for the said variables. Clinically diagnosed EOS had a prevalence rate of 13% while culture-positive EOS had a prevalence rate of 0.34%. A table was used to show the clinically septic neonates who were pEOScalc and nEOScalc. A sub-analysis was done to show culture-positive septic neonates who were pEOScalc and nEOScalc. Data were compared with the results of the non-septic group.

## RESULTS

A total of 3,318 neonates were born between January 2019 and March 2021. Of these, 245 septic neonates met the inclusion criteria and an equal number of 245 non-septic neonates were included as controls, as summarized in Table 1.

Table 1. Clinical Characteristics of Septic and Non-Septic Neonates

| Clinical Characteristics | | Septic Neonates n = 245 | % | Non-Septic Neonates n = 245 | % | p-value |
|---|---|---|---|---|---|---|
| Age of Gestation (AOG) | 35-36 weeks | 25 | 10.2 | 9 | 3.7 | 0.00* |
| | 37-38 weeks | 100 | 40.8 | 112 | 45.7 | 0.28 |
| | 39-40 weeks | 111 | 45.3 | 122 | 49.8 | 0.32 |
| | 41-42 weeks | 9 | 3.7 | 2 | 0.8 | 0.03* |
| Gender | Male | 138 | 56.3 | 125 | 51 | 0.24 |
| | Female | 107 | 43.7 | 120 | 49 | 0.24 |
| Birthweight | < 1500 g | 1 | 0.4 | 0 | 0 | 0.32 |
| | 1500-2499 g | 31 | 12.7 | 14 | 5.7 | 0.01* |
| | 2500-3500 g | 191 | 77.9 | 192 | 78.4 | 0.91 |
| | >3500 g | 22 | 9 | 39 | 15.9 | 0.02* |
| Apgar score at 5 minutes of life | <5 | 7 | 2.9 | 4 | 1.6 | 0.36 |
| | >5 | 238 | 97.1 | 241 | 98.4 | 0.36 |

*Difference is Significant at Z-test for 2 sample proportions p-value <=0.05
Hypothesis tested using 2-tailed test

Neonates in both groups were between 39-40 weeks AOG. More septic neonates were noted in the 35-36 (p-value 0) and 41-42 (p-value 0.03) weeks group. There is a slight male preponderance in both groups with 56.3% (138) for the septic group and 51% (125) for the non-septic group, but this was not statistically significant (p-value 0.24). Birthweights mostly fell between 2500 to 3500 grams. Septic neonates were noted to have lower weight ranges with a significant difference in the 1500-2499 grams (p-value 0.01) group, while more non-septic neonates weighed >3500 grams. As for the APGAR score at 5 minutes of life, the septic neonates had lower scores, but this was not statistically significant (p-value 0.36).

Table 2. Maternal Risk Factors associated with EOS in Septic Neonates and Non-Septic Neonates

| PARAMETER | | Septic Neonates | | Non-Septic Neonates | | Total | Mean |
|---|---|---|---|---|---|---|---|
| Gestational Age | Weeks AOG | 34 - 42 2/7 | | 32 - 42 2/7 | | 32– 42 2/7 | - |
| Highest Maternal temperature | ºC | 36.0 - 38.8 | | 36.0 - 38 | | 36.0 - 38.8 | 37.4 |
| Duration of rupture of membranes | Minutes (m) – Hours (h) | 3 m – 240 h | | 2 m – 28 h | | 2 m – 240 h | 120 h |
| PARAMETER | | n = 245 | % | n = 245 | % | n = 490 | % |
| Group B streptococci colonization | Negative | 41 | 16.7 | 43 | 17.6 | 84 | 7.1 |
| | Positive | 0 | 0 | 0 | 0 | 0 | 0 |
| | Unknown | 204 | 83.3 | 202 | 82.4 | 406 | 82.9 |
| Type and duration of initiation of antibiotics prior to delivery | Broad spectrum > 4 hrs prior to birth | 37 | 15.1 | 22 | 9 | 59 | 12 |
| | Broad spectrum 2-3.9 hrs prior to birth | 3 | 1.2 | 13 | 5.3 | 16 | 3.3 |
| | GBS specific > 2 hrs prior to birth | 81 | 33 | 24 | 9.8 | 105 | 21.4 |
| | No or any < 2 hrs prior to birth | 124 | 50.6 | 186 | 75.9 | 310 | 63.3 |

Table 2 provides the maternal characteristics and risk factors of mothers of both septic and non-septic neonates. The non-septic group had a wider gestational age range from 32 to 42 2/7 weeks compared with the septic group (34 to 42 2/7 weeks). The highest maternal temperature was noted in the septic group (38.8˚C), compared to 38˚C in the non-septic group. The duration of rupture of membranes was longer in the septic group (240 hours), compared to 28 hours in the non-septic group.

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For both groups, maternal GBS status was mostly unknown (82.9%) and majority had either no antibiotics or received the dose less than 2 hours before delivery (63.3%).

Table 3. Number of Culture Positive Sepsis

| Blood Culture Positive Result | n = 15 | % |
|---|---|---|
| Methicillin Resistant *Staphylococcus epidermidis* | 6 | 40 |
| Methicillin Sensitive *Staphylococcus epidermidis* | 2 | 13.3 |
| Methicillin Resistant *Staphylococcus haemolyticus* | 2 | 13.3 |
| Methicillin Resistant *Staphylococcus hominis* | 1 | 6.7 |
| Methicillin Resistant *Staphylococcus warneri* | 1 | 6.7 |
| *Streptococcus mitis* | 1 | 6.7 |
| *Corynebacterium sp.* (diphtheroids) | 1 | 6.7 |
| *Pseudomonas stutzeri* | 1 | 6.7 |

Of the 245 septic neonates, only 15 had positive culture results (Table 3). The most common isolates are methicillin-resistant *Staphylococcus epidermidis* in 6 neonates (40%), methicillin-sensitive *Staphylococcus epidermidis in 2* (13.3%) and methicillin-resistant *Staphylococcus haemolyticus* (13.3%) in another 2.

Of the 245 septic neonates, six (2.45%) had an abnormal CBC and 14 (5.7%) had elevated CRP, but all had negative culture results. The non-septic neonates had normal CBC and CRP.

Based on the NEOSC, 64 (26%) of 245 clinically septic neonates were pEOScalc, while 181 (74%) were nEOScalc (Table 4). Of the 245 non-septic neonates, 3 (1.2%) were pEOScalc while 242 (98.8%) were nEOScalc. The calculated average EOS risk at birth is 0.24/1000 live births for the septic and 0.12/1000 live births for non-septic neonates.

Table 4. Comparison of the Septic Neonates and Non-Septic Neonates who were pEOScalc and nEOScalc in the NEOSC

| EOS Calculator Outcome | Actual Clinical Outcome (Clinical Sepsis) *Gold standard | | | | Total |
|---|---|---|---|---|---|
| | Septic Neonates | | Non-Septic Neonates | | |
| | n =245 | % | n = 245 | % | |
| pEOScalc | 64 | 26 | 3 | 1.2 | 67 |
| nEOScalc | 181 | 74 | 242 | 98.8 | 423 |
| Total | 245 | 100 | 245 | 100 | 490 |

Based on the calculator, of the 15 culture positive septic neonates (Table 5), four (26.7%) were labeled positive for sepsis (pEOScalc) while 11 (73.3%) were negative (nEOScalc). The calculated average EOS risk at birth for culture-positive septic neonates is 2.87per 1000 live births.

Table 5. Number of Culture Positive Septic Neonates and Non-Septic Neonates who were pEOScalc and nEOScalc in the NEOSC

| EOS Calculator Outcome | Actual Clinical Outcome (Culture positive) | | | | Total |
|---|---|---|---|---|---|
| | Septic Neonates | | Non-Septic Neonates | | |
| | n =245 | % | n = 245 | % | |
| pEOScalc | 4 | 26.7 | 3 | 1.2 | 7 |
| nEOScalc | 11 | 73.3 | 242 | 98.8 | 253 |
| Total | 15 | 100 | 245 | 100 | 260 |

With a 95% confidence interval (CI), the computed sensitivity (Table 6) is 26.12% (20.74% to 32.10%), specificity at 98.78% (96.46% to 99.75%), positive likelihood ratio at 21.33 (6.79 to 66.99) and negative likelihood ratio at 0.75 (0.69 to 0.81). Positive predictive value is at 76.12% (50.38% to 90.92%) while negative predictive value is at 89.95% (89.24% to 90.61%). The accuracy of the EOS risk calculator is 89.33% (86.25% to 91.92%).

Table 6. Calculated Outcome from the Online Statistical Medical Calculator using the Clinically Diagnosed Septic Neonates (Gold Standard) and Non-Septic Neonates

| PARAMETER | 95% CI | Value |
|---|---|---|
| Sensitivity | 26.12% | 20.74% to 32.10% |
| Specificity | 98.78% | 96.46% to 99.75% |
| Positive Likelihood Ratio | 21.33 | 6.79 to 66.99 |
| Negative Likelihood Ratio | 0.75 | 0.69 to 0.81 |
| Disease prevalence | 13.00% | |
| Positive Predictive Value | 76.12% | 50.38% to 90.92% |
| Negative Predictive Value | 89.95% | 89.24% to 90.61% |
| Accuracy | 89.33% | 86.25% to 91.92% |

*Available at Calculated via MedCalc

## DISCUSSION

Globally, sepsis remains to be one of the major causes of morbidity and mortality in neonates, with EOS being 2.6-fold more common than late-onset sepsis (LOS).[9]

According to the WHO report on the epidemiology and burden of sepsis as of 2020, there are 1.3 to 3.9 million annual neonatal sepsis cases and 400,000 to 700,000 annual deaths worldwide. An estimated 84% of neonatal deaths due to infections could be prevented through early diagnosis and timely, appropriate clinical management.[9] Among the causes of death is EOS with an incidence of 7.1 to 38 per 1000 live births in Asia.[10]

Currently, blood culture is the gold standard for diagnosis of EOS, but only less than 1% of neonates are culture positive.[2] In addition, the incidence of culture-proven EOS in newborns only ranges between 0.5 to 1.2 cases per thousand live births.[3] Obtaining blood cultures may also result in infant discomfort and parental anxiety. With these limitations, EOS is frequently considered based on nonspecific clinical presentation.[2] In this study, only 15 of 245 septic neonates were culture positive; thus, the clinical diagnosis of EOS which is the actual outcome of the neonate (consistent with the description in the *Standards of Newborn Care)* is the substitute gold standard and was compared to the non-septic neonates (control).[5]

Based on the clinical characteristics of the septic and non-septic group, it was noted that more septic neonates were in the late preterm (35-36 weeks) and late-term (41-42 weeks) groups. More septic neonates were also noted to have lower weight ranges. These are consistent with literature showing that those born prematurely with lower birth weights are at a higher risk for infection. In contrast, there were more non-septic neonates who were >3500 grams and these were term neonates with fewer risk factors.

The EOS risk calculator, a risk-based prediction model for identifying neonates at risk for EOS, may dramatically reduce the number of infants who require extensive evaluation and antibiotic therapy. This in turn could lead to decreased healthcare costs associated with sepsis workups, antibiotic administration, and hospital stay.[2]

Based on available evidence, the NEOSC is a unique and promising tool which can be utilized in the newborn population as it allows healthcare providers to estimate the EOS risk score with a patient-specific probability to determine how to proceed in evaluating and empirically treating the neonate for EOS.

Several studies debated on the safety of applying the NEOSC to accurately recognize all EOS neonates, especially those who are asymptomatic. In a retrospective study done by He, *et al*. in Chongqing, China, the EOS calculator (sensitivity: 81.16%, specificity: 93.92%) has shown good predictive value and that alone or in combination with blood biomarkers can promote early and accurate recognition of EOS and help limit unnecessary antibiotic exposure.[11] On the other hand, a meta-analysis on the sensitivity of the EOS risk calculator by Pettinger, *et al*. demonstrated that the probability of the calculator missing a case of EOS was best case 0.19 [0.11-0.29] and worst case: 0.31 [0.17 - 0.49], and that a large proportion of true cases of EOS were missed by the calculator.[12]

Previous studies investigated the performance of the NEOSC which mostly involved well-developed and high-income countries where GBS screening of mothers is a standard.[4,12] With the GBS status of mothers being a major variable in the NEOSC, this study investigated if it will perform similarly when data about GBS status is not available. In our study it demonstrated poor sensitivity (Sn 26.12%) in detecting EOS. It failed to recommend treatment in at least 181/245 (74%) neonates with clinically diagnosed EOS and 11/15 (73.3%) neonates who were culture positive for EOS.

With its low sensitivity, it is not recommended as a screening tool as it would miss a significant number of septic neonates. However, with its high specificity (Sp 98.78%), the calculator may aid in the confirmation of EOS since non-septic or well-appearing neonates will be correctly identified through the calculator.

Additionally, it demonstrated a high positive likelihood ratio, which emphasizes that the calculator is to be used more for confirmation than for screening. With its negative likelihood ratio (0.75), positive predictive value (76.12%) and negative predictive value (89.95%), this tool can predict the probability of those truly not having sepsis with an accuracy calculated at 89.33%.

It is hard to quantify whether the benefits of reducing antibiotic use outweigh the occasional miss in the calculator since estimating the effects of widespread (over)use of antibiotics on individuals and populations is difficult. Kuzniewicz, *et al.* argued that any potential delays in treatment are far outweighed by the dramatic reduction in antibiotic use.[4]

The calculator may provide an objective assessment of symptomatic versus asymptomatic infants, but the ultimate decision is made by the physician. Studies reported several infants with culture-positive sepsis with an initially low sepsis risk score who clinically deteriorated beyond the 12th hour of life. This highlights the need to incorporate risk factors with continuous clinical monitoring in the first 24 hours of life.[2] No method for predicting EOS is perfect, and there is no substitute for clinical monitoring since there will inevitably be some neonates without identified risk factors for infection who develop sepsis.

Considering the global health burden associated with over-investigation and possible over-treatment of EOS, it is recommended for future studies to do modification of the variables and assessment of its accuracy in both high income and low to middle-income countries through multicenter research. One of the parameters in the NEOSC is the GBS status of mothers, which is not determined routinely in our setting; thus, a prospective study design could also be done to include this data. It is recommended to evaluate the predictive abilities of other maternal risk factors (e.g., Urinary Tract Infection, COVID-19, and Upper Respiratory Tract Infections).

A study to compare the diagnostic accuracy of the NEOSC with culture-positive neonates as the control group is also recommended.

## CONCLUSION

The diagnostic accuracy of the NEOSC in screening for EOS in neonates more than 35 weeks age of gestation was 89.33%. In addition, the sensitivity demonstrated by the NEOSC in this study indicated that it is poor in identifying neonates at risk for EOS, thus limiting its use as a screening tool. The calculator appears more likely to miss cases and has failed to recommend treatment in at least 74% of clinically septic neonates and 73.3% of culture-positive septic neonates. The calculator may be used as an adjunct to clinical and laboratory parameters to support the diagnosis of neonatal sepsis since it has a high specificity (98.78%).

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